Mitesh Kumar Dwivedi
A. Sankaranarayanan
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Role of Microorganisms in Pathogenesis and Management of Autoimmune Diseases

Volume II: Kidney, Central Nervous System, Eye, Blood, Blood Vessels & Bowel

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Foreword

Over 70 years ago Rose and Witebsky demonstrated autoimmune disease by inducing thyroiditis in a rabbit. From that time our understanding of autoimmune disease has continued to evolve. Increasingly, gene variants associated with regulating the immune response have been found to confer susceptibility to the development of autoimmune disease. But for most autoimmune diseases, genetic susceptibility is not enough on its own to cause disease but requires an additional environmental signal of which microorganisms are a leading candidate. Evidence suggests that microorganisms are particularly positioned to promote autoimmunity that leads to autoimmune disease because many of the susceptibility variants associated with autoimmune disease are components of the innate immune response that occurs with infection. Linking an infection to an autoimmune disease has been difficult to prove because there is usually an extended period of time between the infection and the appearance of clinical autoimmune disease. The best evidence that infectious agents can cause autoimmune disease comes from animal studies such as when viruses are used to induce the autoimmune disease myocarditis. Recent clinical evidence has bolstered the argument by finding that Epstein-Barr virus infection precedes the development of multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus and SARS-CoV-2 infection leads to myocarditis, antiphospholipid syndrome, Guillain-Barré syndrome, and Kawasaki disease, for example.

Despite progress in the diagnosis and treatment of many autoimmune diseases, the prevalence, incidence, and complications associated with many autoimmune

diseases continue to climb. With so many advances we are successfully able to manage—but not cure—many autoimmune diseases. Future breakthroughs in understanding autoimmunity will need to merge ideas from both the clinical and experimental basic research fields. Experts in autoimmune diseases of the kidney, central nervous system, eye, blood, blood vessels and bowel have contributed in this book to provide the latest information and insights on the pathogenesis of disease and the role of microorganisms including the gut microbiome in promoting or regulating disease. Part I provides an overview of autoimmunity and the gut microbiome with recent findings related to COVID-19 and vaccine-induced autoimmunity. Part II provides a detailed description of the role of microorganisms in the pathogenesis and management of autoimmune diseases that affect the kidney and adrenal gland. Part III describes microorganisms involved in the pathogenesis of autoimmune diseases that affect the nervous system including the demyelinating autoimmune diseases multiple sclerosis, Guillain-Barré syndrome, neuromyelitis optica and acute disseminated encephalomyelitis and their management. Part IV describes the pathogenesis and management of inflammatory bowel diseases while Part V describes autoimmune blood and blood vessel disorders. Part VI describes microorganisms involved in the pathogenesis and management of autoimmune eye diseases while Part VII with type I diabetes. And finally, Part VIII provides an overview of the current challenges and future prospects in research for therapies that target microbial pathomechanisms. This volume will be enormously useful to clinicians and basic researchers alike who seek to better understand the relationship of infections to a particular autoimmune disease and to the field as a whole.

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Preface

The book *Role of Microorganisms in Pathogenesis* and *Management of Autoimmune Diseases* is focused on how microbial pathogens can subvert the immune system into responding against self so resulting in the development of autoimmune disease against specific organs or tissues. Importantly, the understanding that the book provides, with respect to the role of microorganisms in autoimmunity, can aid in the design of therapeutic strategies.

This book consists of eight parts. The first part overviews the current understanding of the human microbiome, its link with autoimmunity, and the role of vaccines in the triggering of autoimmune responses. Subsequent parts cover the role of different microbes in causing autoimmune diseases of the kidney, central nervous system, eye, blood, blood vessels and bowel. Moreover, their role in the management and/or prevention of the above-mentioned disorders is also put forward. The final part covers the current challenges in researching microbial pathomechanisms in relation to autoimmune diseases, the relationship between genetic susceptibility and the gut microbiota in the development of autoimmunity, and probiotic-based treatments for autoimmune disease.

We, the editorial team, strongly believe that the contents of the individual chapters will provide recent and updated information as well as new insights into the interrelation of microbes and autoimmunity. As such, the book will be useful in education and as a scientific tool for academics, clinicians, scientists, researchers and health professionals in various disciplines including microbiology, medical microbiology, immunology, biotechnology and medicine.

As the editors, we would like to express our sincere gratitude to all authors for their excellent contributions. We are also indebted to the publishers for their efforts to publish the book in a timely fashion.

Surat, Gujarat, India — Mitesh Kumar Dwivedi
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Sheffield, UK — E. Helen Kemp
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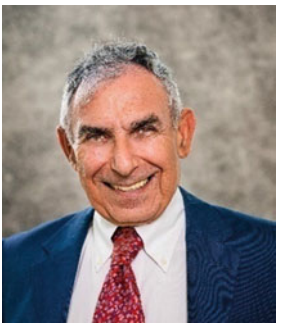
Editors and Contributors

About the Editors

Mitesh Kumar Dwivedi is an Assistant Professor of Microbiology at C. G. Bhakta Institute of Biotechnology, Uka Tarsadia University. He has published 60 research papers in reputed journals, written 42 book chapters, and is the editor of six books. He has an *h*-index of 23 with 1852 citations for his research papers. He has more than 15 years of experience in research and teaching in various allied fields of microbiology and immunology. He has contributed significantly to the field of vitiligo—a skin autoimmune depigmenting disorder. His current research interests include investigation of immunogenetic, autoimmune and therapeutic aspects of vitiligo, rheumatoid arthritis, sickle cell disease and the role of probiotics in ameliorating the autoimmune diseases. He has been serving as an editorial board member and reviewer of many international journals. He has been honoured with many international and national awards for his excellent research performance [DST-SERB Core Research Grant (2022), Best Researcher Award (2020), INSA Visiting Scientist Award (2019), DST-SERB Early Career Research Award (2018), Young Scientist Awards (2011, 2013, and 2018)] and secured all India rank "32" in CSIR-NET National examination (2011; Life Sciences). He has successfully completed research projects from national funding agencies such as SERB-DST, GUJCOST, UTU, and Neosciences & Research Solutions Pvt. Ltd. and guided students for their doctoral and master's degrees.

A. Sankaranarayanan is an Associate Professor in the Department of Life Sciences, Sri Sathya Sai University for Human Excellence, Kalaburagi, Karnataka, India, from June 2021 onwards. His current research focus is on fermented food products. He has published ten books, 35 chapters, 63 research articles in international and national journals of repute, guided five PhD and 16 MPhil scholars and operated five minor funded projects in microbiology. From 2002 to 2015, he worked as an Assistant Professor & Head, Department of Microbiology, K. S. R. College of Arts & Science, Tiruchengode, Tamil Nadu, and August 2015 to May 2021 associated with Uka Tarsadia University, Surat, Gujarat, India. He was awarded with Indian Academy of Sciences (IASc), National Academy of Sciences (NAS) and the National Academy of Sciences (TNAS) sponsored summer research fellowship for young teachers consecutively for 3 years and his name is included as a Mentor in DST-Mentors/Resource persons for summer/winter camps and other INSPIRE initiatives, Department of Science & Technology, Govt. of India, New Delhi. He is a Grant reviewer for British Society for Antimicrobial Chemotherapy (BSAC), UK.

E. Helen Kemp completed her PhD in Microbiology at the University of Warwick and the Centre for Applied Microbiology and Research, Salisbury, in 1988. Since 1989, she has worked at the University of Sheffield as a Research Fellow in the Medical School. She has long-standing interests in the autoimmune and genetic aspects of the depigmenting disease vitiligo, characterising autoimmune responses against the calcium-sensing receptor in patients with parathyroid autoimmunity, and the aetiology of autoimmune thyroid disease. She has published more than 70 research papers in these areas of research and has contributed to books and review articles in the field of autoimmunity.



Yehuda Shoenfeld, MD, FRCP, MaACR, is the founder and head of the Zabludowicz Center for Autoimmune Diseases, at the Sheba Medical Center, which is affiliated to the Sackler Faculty of Medicine in Tel-Aviv University, in Israel. Professor Shoenfeld was also the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at the Tel-Aviv University. Professor Shoenfeld's clinical and scientific works focus on autoimmune and rheumatic diseases, and he has published more than 2250 papers in reputed journals. His articles have had over 130,000 citations. His Scopus h-index is 123. He has written more than 350 chapters in books and has authored and edited 35 books, some of which became cornerstones in science and clinical practice.

Professor Shoenfeld is on the editorial boards of 43 journals in the field of rheumatology and autoimmunity and is the founder and the editor of four high impact factor journals related to autoimmunity, science and medicine. Professor Shoenfeld received the EULAR prize in 2005, in Vienna, Austria: "The infectious aetiology of anti-phospholipid syndrome," and received a gold medal from the Slovak Society of Physicians for his contribution to Israel–Slovakia collaboration (March 2006). He is also an honorary member of the Hungarian Association of Rheumatology and the Royal Society of Physicians (UK). In UC Davis, USA, Professor Shoenfeld received the Nelson's Prize for Humanity and Science for 2008. In 2009 he was honoured as Doctoris Honoris Causa, from Debrecen University (Hungary) and Hasselt University in Belgium (2018) and from 2009 he is an honorary member of the Slovenian National Academy of Sciences. He was recently awarded a Life Contribution Prize in Internal Medicine in Israel, 2012, as well as the ACR Master Award in 2013. In 2018, he was elected to the Israeli Academy of Sciences, and in 2021 he was nominated as a **President of the Ariel University in Israel**. Professor Shoenfeld has educated a long list of students with >55 becoming heads of departments and institutes.

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Part I

Human Microbiome, Vaccines and Autoimmunity

Autoimmunity and Microbiome

1

Elena Soto-Vega and Jose Yunam Cuan-Baltazar

Abstract

The interaction since the birth of the microbiome with the immune system influences the development of autoimmune disorders. The cross-talk between microbiota and the immune system regulates innate and adaptative homeostasis in the mucosa. In a genetically susceptible individual, the imbalances between the microbiota and immune system in certain environmental contexts could contribute to the pathogenesis of autoimmunity. Compositional and metabolic changes of microbiota have been reported in autoimmune diseases, the evidence suggests that dysbiosis contributes to the disease pathogenesis. The autoimmune mechanisms proposed to be associated with microbiome include abnormal microbial translocation, molecular mimicry, and dysregulation of the microbiome.

Keywords

Microbiota · Microbiome · Immune system · Autoimmunity

1.1 Introduction

Autoimmune diseases are characterized by a hyperactive immune response against self-proteins and tissues. The etiology of autoimmune diseases is unknown, since these pathologies are multifactorial, it has been proposed that genetic and environmental factors have an important role to trigger the disease, the estimated autoimmunity incidence is around of 3–5% worldwide.

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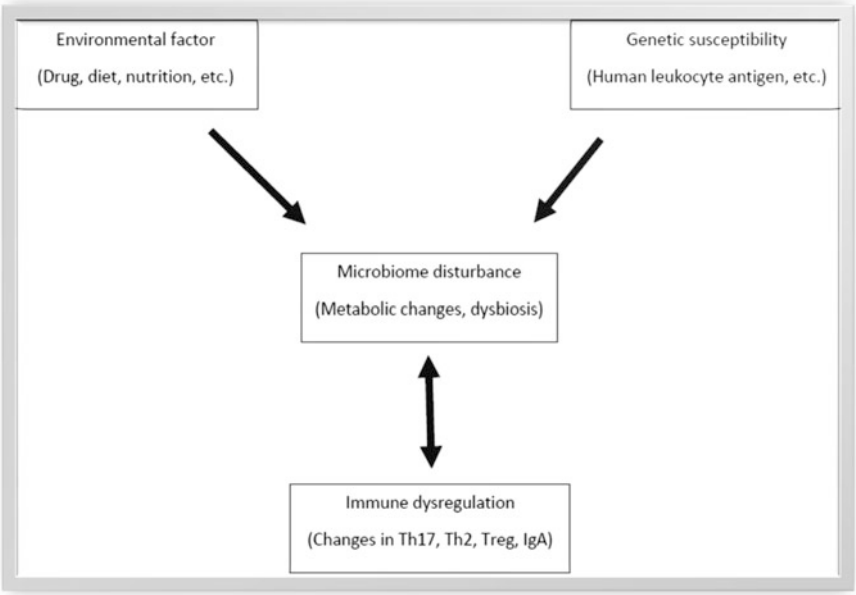

Fig. 1.1 Autoimmune disease is influenced by environmental factors and host genetic susceptibility. Aberrant interactions between the microbiome and the host's immune system contribute to the development of various immune-mediated disorders. The microbiome alterations are associated with aberrant mucosal immune responses, including unregulated Th17, Th1, and Th2 responses, downregulated Treg and dysregulated humoral immunity; this may finally result in autoimmunity

The study of the microbial communities of bacteria, viruses, fungi, and protozoa that inhabit the human have gained attention. It is known that the microbiome impacts health and disease, the microbial communities play a role in the nutrient synthesis and energy harvest of food, and it has been shown that the microbiome regulates the innate and adaptive immune responses (Fig. 1.1).

The microbiota is located mainly in the mucous membranes (the gut, the lungs, skin, vagina, eyes, ear, oral cavity, sinonasal compartment, and placenta). The mucosal colonization by microbiota is a dynamic, complex, and gradual process that begins in the first years of life. The innate immune development is influenced by maternal microbiota transfer, as its metabolite. The microbiome colonization is modulated by the birth delivery mode, breastfeeding, and food introduction. The microbiota will be modified by factors such as diet, antibiotics, drugs use, age, or disease (Zamudio-Vázquez et al. 2017; Gómez de Agüero et al. 2016) (Table 1.1).

The host immune system controls microbial communities, and the microbiota produces biochemically compounds, such as neurotransmitters and tryptophan-derived metabolites, influencing the maturation and activity of the immune system (Wikoff et al. 2009). The microbiota composition and its correlation with health/disease is a multifactorial process, and its balance is essential to maintain the host's health. The alteration in microbiota composition (Dysbiosis) produces homeostatic

Table 1.1 Factors (since birth) that modify the microbiota composition

Born by caesarea	Born vaginally	Formula-fed	Breast fed
Decreased bacterial colonies	Increased *Bifidobacterium* and *lactobacillus*	Increased colonization of *bacteroides*, *bifidobacterium*, *enterobacteriaceae*, and *streptococcus*	Almost exclusively *bifidobacterium*, *lactobacillus*, *B. longum.*
Decreased diversity			
Risk of colonization by *clostridium*			

changes in the immune system and some of them have been correlated with autoimmune disorders, for example, type I diabetes, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, Chron's disease, ulcerative colitis, Behcet's disease, autoimmune skin condition like vitiligo, Pemphigus Vulgaris, atopic dermatitis and autoimmune neurological diseases (Gianchecchi and Fierabracci 2019).

Human gut microbiota is composed of almost 100 trillion microorganisms from over 500 genera of bacteria, the main phyla that colonize the gut are the *Firmicutes* and *Bacteroidetes*. The human microbiome varies depending on its location, oxygen concentration, nutrient availability, temperature, and exposure to the immune system, for example, the gut microbiota undergoes changes from the mucosal to the luminal/fecal side (Khan and Wang 2020).

1.2 Microbiota and Immune System Interaction

The first exposure of the immune system to the microbiota is during birth and have a profound and long-term implication in human health, this interaction will set the relation between the immune system and microbiota. The colonization will continue during the first years of life and is related to the maternal interaction like the breast milk, which contains live microbes, metabolites, IgA, as well as, cytokines, this will promote the expansion of the constituents of the microbiota such as *Bifidobacterium* (Marcobal et al. 2010; Marcobal and Sonnenburg 2012) (Table 1.1). The gut microbiome composition becomes stable around the third year of life but can be reshaped (diet, lifestyle, diseases, among others).

The germ-free (GF) animal models are used to study the relationship between the microbiota and the immune system; the absence of microbiota is associated with defects in the lymphoid tissue associated with the mucosa, for example, the population of intraepithelial lymphocytes (IELs) and T cells is reduced, and there is an absence of Th17 lymphocytes. The B lymphocytes population is affected leading to an alteration of the immunoglobulin repertoire. The conclusion obtained with these

animals is that the extracellular signals from the microbiota are necessary for the development of the immune system.

The mucosal colonization is characterized by an inflammatory cytokine production that activates the T and B cells to generate a regulatory response. The interactions between the immune system and microbiota is mediated by the recognition of the conserved microbial associated molecular pattern (MAMPs). Epidemiological observations revealed that alteration of the microbiota in the mother or neonates may predispose to diseases associated with dysregulated barrier responses such as asthma (Ege et al. 2011).

The innate immune cells are distributed at the interface of the mucosa, and tissue, its main function is to sense the microbiome components or products and produce signals, which are important because are used by the immune system to control the homeostasis between the host and the microbiome. The homeostasis is essentially regulated by the minimum contact of microbiota and the epithelial cell, which is achieved mainly through the mucus, limiting tissue inflammation, and microbial translocation. In physiological situations, no bacteria are in contact with the intestinal epithelial cells, except at the tips of the villi for segmented filamentous bacteria. In the presence of pathogenic microorganisms, the microbiota contributes to the stimulation of mucus production and occupies the binding sites available on the mucins, impeding pathogen adhesion.

The comparative studies between patients and healthy controls have shown differences in the microbiome composition, for example, the presence of *Bacteroides fragilis*, and *Clostridium* favors the differentiation of T lymphocytes, the production of IL-10, and the secretion of some polysaccharides that bind the intestinal barrier, the expression of TGF-β in the colon, and the secretion of Immunoglobulin E (IgE) (Cavalcante-Silva et al. 2015).

In murine models, the changes of the intestinal microbiome composition cause a state of insulitis, with an increase in the expression of the lymphocytic regulatory factors like transcription factor forkhead P3 (FOXP3) in the T cells in the pancreas, and a decrease of these cells in the ileum and colon; an increase on IL-7 and INF-γ in T $CD4^+$ lymphocytes in the pancreatic lymph nodes. In humans with type 1 diabetes, changes in their microbiota have been reported, like an increase in the populations of *Clostridium*, *Bacteroides*, and *Veillonella*, and a decrease of *Bifidobacterium* and *Lactobacillus*. In addition, these patients had less diversity in their microbiota composition (Vaarala 2013).

The first line of defense in the small and large intestines is provided by the mucous which is a natural biological selective habitat for the microbiota, due to the presence of mucin glycans, which serve as attachment sites for bacteria. The mucosal integrity is essential for the homeostasis. The mucus is an aqueous and viscoelastic secretion, composed of water (90–95%), electrolytes, lipids (1–2%), proteins, and others. The mucus composition, viscosity, thickness, and penetrability, is a complex mechanism, the expression, synthesis, secretion, degradation, glycosylation, and structure of mucins, are modified by the host response to microbiota (Paone and Cani 2020).

The presence of specific bacteria shapes the glycan profile of the mucus and are associated with many glycosyltransferases. The lipopolysaccharides (LPS) and peptidoglycans stimulate mucus secretion.

The intestinal mucus layer is dynamic, mucin transcription factors are regulated at the transcriptional and epigenetic level, and they can be linked to specific bacteria or microbial products such as LPS, Flagellin, lipoteichoic acid, and lipopeptide. All of them mostly act through the activation of nuclear factor (NF)-kB, which has been shown to have a binding site in the promoter of MUC2, also other inflammatory markers (TNF-α, Serum amyloid A3 and interleukins such as IL-1β, IL-4, IL-13, and L-22) stimulate the transcription of MUC2. The primary function of the MUC2 is provide a protective barrier between the epithelial surfaces and the gut lumen. The epigenetic study of colon cancer has shown that the methylation of CpG islands in specific regions of MUC2, DNA methylation, or histone modifications but also micro-RNAs contribute to the complex regulation of MUC2 expression.

The mucus function associated with microbiota are: (1) The glycosylated mucins serve as food sources. (2) The spatial structure provided by mucin gel networks helps microbiota carve out specific niches. (3) The mucins serve as virulence-attenuating signals.

The Paneth cells and enterocytes produce antimicrobial peptides (AMP), with functions like sequestering key growth nutrients, permeabilizing bacterial membranes among other mechanisms. One functions of these AMP is facilitate the microbiota biodiversity, and the communication or cooperation between bacterial strains this interaction shapes the microbiome composition (Muniz et al. 2021). Some examples of antimicrobial peptides in the gut are defensins, cathelicidins, and regenerating genes (Reg)III (Reg3α or Reg III), all are soluble lectin that interacts with bacterial surface components.

Defensins are the most abundant cationic peptides, their function is to create small pores in the bacterial membrane, the microbiota can induce the secretion of defensin through the release of butyrate, lactic acid among other metabolites. The Paneth cells secrete β-defensins and epithelial cells produce α-defensins. The immune cells (B and T lymphocytes, macrophages, monocytes, and dendritic cells) produce both α- and β-defensins.

Cathelicidins are cationic peptides derived from macrophages and colonic epithelial cells, and its function is controlling the microbiome composition through the disruption of the bacterial membrane.

The bacteriocins are substances produce by the bacterial and its function is disturbing protein, RNA and DNA metabolism, and bacterial membranes; These bacteriocins participate in the establishment of microbes within the microbiota.

Immunoglobulin A (IgA) is the main antibody in mucosal secretions and is vital in the defense against pathogenic microorganisms. The main IgA function is neutralizing toxins and viruses, blocking excessive live bacteria, adherence or translocation, clearing unwanted macromolecular structures at the epithelial surface, and directed sampling of luminal antigen. The IgA participates to maintain the microbiota diversity. In mice, the IgA deficiency increases inter-individual variability in the microbiome and decreases diversity. The most common human

immunodeficiency is the lack of IgA, and it does not affect lifespan, only increases susceptibility to respiratory and gastrointestinal infections (Donaldson et al. 2018).

The T cell has a complex and dynamic cross-talk with the microbiota. Most $TCD4^+$ cells reside in tissues colonized by microorganisms. The gut resident $TCD4^+$ cells have receptors that recognize microbiota, these cells are essential for microbiota-specific IgA response, involved in microbiota homeostasis and colonization. Microbiota can modulate the $TCD4^+$ compartment inducing different T cell subsets into four large categories: Th1, Th2, Th17, and Treg (Brown et al. 2019).

In Peyer's patches, the $Foxp3^+$ Treg cells and follicular helper T cells (Tfh) promote the class switch of B lymphocytes to IgA, with the finality of compartmentalizing and regulating the microbiota. Depending on which bacterial participates in the colonization, the differentiation of T lymphocytes will take place, for example, segmented filamentous bacteria colonization elicits signaling via the ILC3/IL-22/SAA1/2 axis to induce IL-17A production by $ROR\gamma t^+$ Th17 cells. The *Bacteroides fragilis* promotes the T $CD4^+$ cell differentiation to balance Th1 and Th2 populations, an effect that relies on polysaccharide A. The polysaccharide A is taken up by lamina propria DCs through a TLR2-dependent mechanism and presented to naïve $CD4^+$ T cells. In the presence of activated TGF-β, these cells can differentiate to T regulatory cells (Tregs), the IL-10 produced by these cells promotes immune homeostasis, contrarily, IL-23 promotes the expansion of proinflammatory Th17 cells (Zheng et al. 2020).

1.3 Microbiota and Autoimmunity

The capacity of microbiota to trigger or promote disease is highly dependent on the immune state of the host, genetic predisposition. The pathogenic mechanism is not well understood, but environmental factors (lifestyle, diet, drugs, and infections) and certain genetic backgrounds have been associated. The study of the microbiome has allowed associated it as a player in the autoimmunity development. The loss of immune tolerance could be produced by microbiota composition changes, process known as dysbiosis. Dysbiosis is defined as a reduction in microbial diversity, and an increase in proinflammatory species, the imbalanced microbiota is unable to protect from pathogenic organisms, and these changes trigger an inflammatory state.

Different mechanisms have been described by which the microbiota could be causing autoimmunity like molecular mimicry, polyclonal T and B cell responses, cross-reacting antigens, formation of neoantigens, and the release of sequestered/cryptic antigens, these mechanisms may be induced by the microbiota or an infection. As mentioned earlier the intestinal microbiota and the immune system senses each other to maintain the homeostasis and responds to pathogens, this interaction is based on tolerance and codependence. The role of T cells is essential to maintain the tolerance, the immunity against pathogens and prevent an inflammatory immune response against the microbiota antigens.

The $CD4^+$ T cell differentiates into functional subsets (Th1, Th2, Th17, and Treg). In autoimmune diseases the balance between Th17/Treg is essential to

maintain homeostasis, it has been described that some microorganisms like *Candidatus savagella* or segmental filamentous bacteria induce a Th17 response. The Th17 cells stimulated by a dysbiosis, secrete proinflammatory cytokines IL-17A, IL-17F, and IL-22 to enforce gut barrier integrity and defense against pathogens. Functional gut barrier disturbance during gastrointestinal infection induces inflammatory anti-commensal T cells that acquire a memory phenotype consistent with pathogen-specific T cells, so environmental insults may trigger anti-commensal responses by the adaptive immune system (Fig. 1.1).

The $CD4^+$ T cell induces B cell proliferation and differentiation in germinal centers, especially follicular helper T cells (Tfh). The activity of Tfh is determined through interactions with microbiota via innate pathways, this interaction between the microbiota and the T cells influences the immunoglobulin repertoire (Dehner et al. 2019). The microbiota elicits both T cell-dependent and T cell-independent IgA.

The metagenomic studies of gastrointestinal disorders like Bowel disease and colorectal cancer have shown alteration in the microbiota, other autoimmune diseases have also been associated with microbiota dysbiosis like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthritis, Sjogren's syndrome, and Behcet's disease, the dysbiosis was stablished comparing the microbiota of patients against healthy people. Some microorganism has been associated to autoimmune diseases (Table 1.2).

The microbiota of autoimmune disease individuals have a different composition compared to healthy subjects, suggesting there is dysbiosis; a reduced diversity of some microbial are correlated with disease, and their accumulation or reduction indicates their potential proinflammatory or anti-inflammatory roles, for example, the increase of *L. salivarius* in the gut of patients with RA or SLE is associated with higher clinical disease activity, the increase of *R. gnavus* is related to lupus nephritis. Reduced diversity and the enrichment of certain species like *Blautia*, *Akkermansia*, and *Clostridiales* are found in RA patients with positive anti-citrullinated antibodies.

1.4 Mechanisms of Autoimmunity Induced by Microbiota

The microbiota may be involved in the generation of autoimmunity through mechanisms like microbiome translocation, molecular mimicry, or dysregulated immune response. Also, it should be considered that individuals with a susceptible major histocompatibility complex haplotype could have a cross-reactive autoimmune response (Greiling et al. 2018).

1.4.1 Microbiome Translocation

Microbial translocation is defined as the movement of microbes and its products from the mucosa into circulation. The integrity of the mucosal barrier is essential to prevent the microbiota trigger the adaptive immune response. Bacterial translocation

Table 1.2 Microbiota alterations observed in the autoimmunity diseases

Autoimmune disease	Observation	Reference
Systemic Lupus Erythematosus	↓ *Firmicutes*, *Bacteroides*, *Lactobacillus*, especially related to *Butyrivibrio* sp. family.	Vieira et al. (2014)
	↑ *Lachnospiraceae*	
Multiple sclerosis	↓ *Bacteroides*, *Parabacteroides*, *Prevotella*, *Lactobacillus*, *Blautia*, *Ruminococcus*, *Bifidiobacterium*	Kirby and Ochoa-Repáraz (2018)
	↑ *Akkermansia.*	
Autoimmune Encephalitis	Some probiotics as *Parabacteroides* and *Akkermansia* were found to be enriched in patients, whereas several pathogens like *Prevotella* were depleted.	Xu et al. (2020)
	The phyla *Proteobacteria* and *Firmicutes* were related to disease severity.	
Rheumatoid Arthritis	The presence of *Prevotella intermedia* and *Porphyromonas gingivalis* in the subgingival dental plaque, as well as synovial fluid, supports a role of microbiota in initiating or maintaining chronic inflammation.	Horta-Baas et al. (2017)
	↑ *Clostridium sp*.	
	↓ *Porphyromonadaceae* and *Bifidobacteriaceae.*	
Ankylosing Spondylitis	↑ *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroideaceae* families.	Konig (2020)
	↓ *Veillonellaceae* and *Prevotellaceae* families	
Psoriasis	↓ Actinobacteria	Sikora et al. (2020)
	↑ *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Staphylococcus*.	
	↑ of *Vibrio*, in the skin	
Psoriatic Arthritis	↓ *Akkermansia*, *Ruminococcus*, *Pseudobutyrivibrio*	Myers et al. (2019)
Type 1 Diabetes Mellitus	↓ of short-chain fatty acids, produced especially butyrate-producing bacteria.	Thomas and Jobin (2020)
	↑ *Zonulin*, *Bacteroideaceae*, *Blautia*, *Rikenellaceae*, *Ruminococcus*, *Streptococcus* and intestinal permeability.	
Grave'sDisease	Presence of antibodies against *Y. enterocolitica* and *H. pylori*.	Fröhlich and Wahl (2019)
	↑ yeast and ↓ in *Bacteroides*.	
Guillain–Barré Syndrome	Related to *Campylobacter jejuni* infection, altering the intestinal microbiota by increasing the gene expression of acetogenesis leading to the conversion of pyruvate to acetate.	Brooks et al. (2017)
Myasthenia Gravis	↓ *Bacteroideaceae* and *Firmicutes*	Qiu et al. (2018)
	↓ *Clostridium*	

(continued)

Table 1.2 (continued)

Autoimmune disease	Observation	Reference
Pernicious Anemia (Autoimmune origin)	↓ *Faecalibacterium prausnitzii* and *Roseburia*, with the ability to produce butyrate and relieve inflammation in the gastrointestinal tract, are reduced in people with the disease.	Xu et al. (2018)
Sjögren's Syndrome	↑ *Firmicutes*, *Streptococcus*, and *Veillonella.*	Moon et al. (2020)
	↓ *Synergistetes* and *Spirochaetes.*	
	Fecal samples ↓ *Faecalibacterium prausnitzii*, one of the predominant butyrate producers in the gut.	
Scleroderma	↓ *Bacteroides*	Volkmann (2017)
	↑ *Firmicutes*, *Clostridium*, *Lactobacillus*, *Prevotella.*	
Celiac Disease	↑ *Firmicutes* and *Proteobacteria.*	Chibbar and Dieleman (2019)
	↓ *Actinobacteria* and *Bifidobacteria*	
Vitiligo	Presence of *Methylobacterium* in lesional skin, and *Anaerococcus*, *Microbacterium* in non-lesional skin	Bzioueche et al. (2021)
Crohn's Disease	↓ *Firmicutes*, *Clostridium cluster IV*, *XIVa*, *XVII* and *Faecalibacterium prausnitzzi.*	Nishida et al. (2018)
	↑ mucolytic and sulfate-reducing bacteria as *Ruminococcus gnavas*, *Ruminococcus torques*, *Desulfovibrio*, and pathogenic bacteria, *Adhesion/ invasive E. coli*.	
Ulcerative Colitis	↑ Proteobacteria (particularly adherent invasive *E. coli*), *Pasteurellaceae*, *Veillonellaceae*, *Fusobacterium* species, and *Ruminococcus gnavus*.	Glassner et al. (2020)
	↓ *Clostridium groups IV* and *XIVa*, *Bacteroides*, *Suterella*, *Roseburia*, *Bifidobacterium* species, and *F. prausnitzii*.	

is promoted by increased intestinal permeability, impaired host defense, and bacterial overgrowth. Changes in intestinal permeability are caused by the loss of tight junction integrity or by cell wall injury at villous tips.

The enterocytes are held together by tight junctions. The movement of bacteria occurs either through the transcellular route involving enterocytes or the paracellular route involving tight junctions. The normal intestinal anaerobic biota is a control mechanism to regulate the translocation of enterobacteria as anaerobic bacteria are not taken up by enterocytes and stay attached to the epithelial receptors.

On the other hand, the movement of bacterial products takes place in enterocytes through the paracellular route. The sources most known of entry of microbes into the circulation from the gut is by direct cellular uptake through the activation of NOD1 receptors in M cells overlying the Peyer's patches by damage to the gut epithelial cells. The bacteria initially adhere to the enterocytes, this allows them to reach the basal membrane. The intestinal lymphatic drainage carries the bacteria to mesenteric lymph nodes from where they spread to other tissues through circulation. Bacterial

components gain access to the systemic circulation via the enteric venous system to the portal vein following lymphatic drainage from the intestine. The LPS released by Gram-negative bacteria acts on macrophages and monocytes to release cytokines, interleukins, and chemokines and activates the complement system, activating both innate and adaptive immune systems, evoking a strong circulating inflammatory response. The Toll-like receptors (TLRs) recognize conserved motifs on pathogens MAMPs, for example, the TLR-2 activated by the peptidoglycan of the Gram-positive bacteria, the TLR-9 recognizes bacterial DNA or the TLR4 that binds LPDS of Gram-negative organisms, other MAMPs are teichoic acids of Gram-positive organisms, glycolipids of Mycobacterium, and viral nucleic acids. Many exogenous MAMPs have been associated with diseases like atherosclerosis, for example, *C. pneumoniae*, *P. gingivalis*, and *Cytomegalovirus* are involved in the development of atherosclerotic plaques. However, bacterial products, such as lipoproteins and heat shock protein 60, could stimulate different TLRs. Some of the biologically harmful effects of LPS include intravascular coagulation, hemodynamic disturbances, metabolic derangements, coronary artery revascularization, vascular endothelial damage, and cholestasis. The TLRs also recognize the molecular patterns of endogenous host material released during tissue damage called damage-associated molecular patterns (DAMPs).

The first evidence of the important of bacterial translocation associated with systemic diseases was in a population prone to obesity and diabetes, it was found that as the population developed diabetes, the bacterial profile in their circulation varied largely, developing a dysbiosis. After that, another dysbiosis has been described as in HIV-positive patients, and cardiovascular diseases. Interestingly, the main microbes associated with these diseases were of the phylum *Proteobacteria* (Vieira et al. 2018; Amar et al. 2013) (Fig. 1.2).

1.4.2 Molecular Mimicry

The molecular mimicry is when a foreign protein has an amino acid sequence homology or similar structural configuration to a self-antigen, then elicits cross-reactive immunity, in autoimmunity, it is recognized that similarity between host and foreign antigens can lead to humoral responses to foreign antigens reacting versus self-antigens and cause disease. The molecular mimicry is postulated to be the initiating event of most autoimmune diseases, a series of molecules and epitopes from pathogens (bacteria, viruses, fungi, parasites) and some harmless nutritional molecules (bovine milk casein) can be the antigen to activates the immune response against a self-antigen. The ability of cross-reacting epitopes to induce autoimmune disease is described in experimental models, some experimental data support the involvement of epitope mimicry in the transient autoimmune syndromes rheumatic fever and Guillain–Barre's disease. More recently, using an in-silico search, amino acid sequence homologies between selected microorganisms with potential pathogenic relevance and thyroid autoantigens were demonstrated (Amar et al. 2013; Avni and Koren 2018).

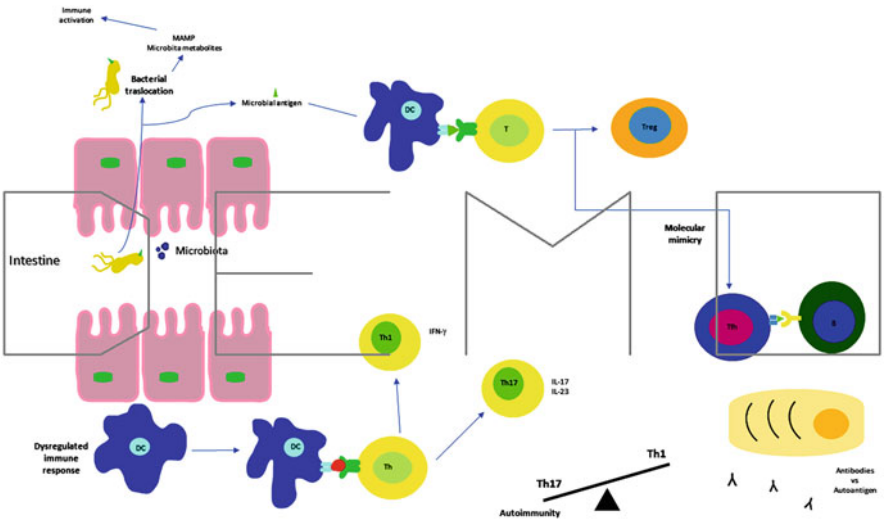

Fig. 1.2 Microbiota and autoimmunity. Some autoimmune diseases have been associated with modifications on the microbiota diversity, which produces a dysregulated immune response, the innate immune cells recognize the microbes, leading the development of autoreactive Th1 and Th17, these cells produce proinflammatory cytokines IL-17 and IL-23, and the INF-γ contributes to autoimmunity. The translocation of microbiomes exposes the immunity system to MAMP and microbiota metabolites that normally are on the mucosal side. During infection, bacterial could induce autoimmunity by cross-reactivity in two ways, the first one bacterial induces self-tissue antigen release and simultaneous presentation of bacterial and self-tissue antigens to T cells; activated T cells produce antibodies against both bacterial and self-tissue antigens, on the other hand, and antigen present in the bacteria could have an amino acid sequence similar to a self-antigen, then the immune response versus the bacterial antigen will act versus a self-antigen

It has been proposed that microRNA could be participate in molecular mimicry, some bacterial proteins may elicit cross-seeded misfolding, inflammation and oxidative stress, and cellular toxicity in the neurodegenerative conformational disorders, initiating or otherwise influencing the development of Parkinson's disease, Alzheimer's disease, and related conditions.

The molecular mimicry leading to cross-reactive T cell recognition is a consequence of the manner of antigen peptide recognition by T cell receptors: the receptor molecule does not screen each amino acid side chain of a peptide, only a few amino acids, therefore different peptides could have a similar sequence of amino acids at a certain position and these are sufficient for the activation of the receptor. Molecular mimicry exists for T cells as well as antibody recognition (Wildner and Diedrichs-Mohring 2020).

Examples of molecular mimicry are the peptides derived from *Bacteroides fragilis*, *Candida albicans*, and *Streptococcus sanguis*, all of which can colonize the human gut, and show similarities with type II collagen, and induced cross-reactive responses in collagen-induced arthritis. *P. copri* has been related to mimic synovial and ribosomal peptides in RA patients. *Bacteroides thetaiotaomicron* and

Roseburia intestinalis can trigger lupus-like symptoms, owing to the homology of their peptides with human Ro60 and β2-glycoprotein I, respectively.

The antibodies directed against the cell wall mannan of the yeast *Saccharomyces cerevisiae* were detected in several autoimmune diseases with different sensibility (RA, SLE, antiphospholipid syndrome), these antibodies are used as a specific serological marker of Crohn's disease (Rinaldi et al. 2013).

The immunogenic ability of microbial peptides is dependent of the particular host HLA-DR genotypes for antigen presentation and recognition. Genetic susceptibility is suggested to be the main predisposing factor for childhood-onset autoimmune diseases, such as juvenile SLE and juvenile idiopathic arthritis. Intriguingly, the microbiota and autoimmunity interplay supports a new hypothesis that the dysregulated postpartum microbiota establishment resulting from abnormal maternal exposure in pregnancy or early-life exposure might also contribute to the early initiation of autoimmune diseases (Fig. 1.2).

1.4.3 Dysregulated Immune Response

Abnormal interactions between the microbiome and the immune system in genetically susceptible individuals contributes to the development of autoimmunity, among other diseases like cardiometabolic diseases and cancer. Dysregulated microbiota and their derivates (such as nucleic acids, polysaccharides, metabolites, and toxins) might trigger an aberrant activation of the immune system, with the consequent upregulation of proinflammatory cytokines (IFN, IL-12, and IL-23, among others) and reduction of anti-inflammatory cytokines (IL-1, TGF-β, among others).

Dendritic cells and macrophages take samples of microbial and antigens from the gut lumen and go to the secondary lymphoid tissues to activate the lymphocyte, normally these interactions between phagocytes and microbiome is part of the immune homeostasis through the Treg. When the microbial sample has proinflammatory derivates, the immune response is reorganized, generating disequilibrium of anti-inflammatory Treg cells and proinflammatory Th17, with and innate immune overreaction and abnormal antigen presentation, which has been implicated in the pathogenesis of Autoimmune diseases. Dysregulated gut microbiota also induces overactivation of B lymphocytes and excessive production of antibodies (Zhang et al. 2020).

The Treg are recognized by their immunosuppressive properties and are essential for microbiota tolerance. The colonization of the mucosa may induce activation of TGF-β in epithelial cells, which stimulates certain subsets of mononuclear phagocytes involved in the induction of Treg differentiation in the mucosa. The microbiota plays a role not only in the development of Treg cell but also in the regulation of Treg by the stimulation of the synthesis of IL-10, the mechanism by which the microbiota induces the synthesis of IL-10 is unknown but is well known that some microorganism induces it like *B. fragilis* through its polysaccharide A,

which produces the induction of IL-10 by the stimulus TLR2-dependent (Kamada and Núñez 2014).

Treg cells are an immunosuppressive sub-population of $CD4^+$ T cells (5–10% of peripheral $CD4^+$ T cells in the blood of healthy individuals), characterized by the expression of the FOXP3. Multiple mechanisms have been described via which Treg exert their suppressive activity and can be broadly classified into four distinct categories:

1.4.3.1 Secretion of Immunosuppressive Cytokines

Inhibitory cytokines, including IL-10, tumor growth factor-β (TGF-β), and IL-35 are abundantly secreted by Treg cells (Table 1.3).

1.4.3.2 Cytolysis

Cytolysis is a Treg cell suppressive mechanism described mainly in cancer and in vitro studies, the targeted cells are driven to apoptosis by Treg cell-secreted granzymes in either perforin-dependent or independent manner.

1.4.3.3 Metabolic Disruption

The Treg cell produces adenosine from the conversion of extracellular adenosine triphosphate (ATP) by the ecto nucleotidases CD39 and CD73 expressed on the cell surface of Treg cells. Adenosine is a metabolite, which suppresses T cells, dendritic cells (DCs), and proinflammatory macrophage maturation and function.

1.4.3.4 Suppression of DC Maturation and Function

A major mechanism of Treg cell-mediated immunosuppression is the inhibition of the immunological synapse between effector T cells and APCs, resulting in impaired APC maturation and T cell anergy. Treg cells, through the expression of inhibitory receptors (e.g., CTLA-4), engage the co-stimulatory molecules CD80/CD86 on DC with a higher affinity than CD28, impeding DC maturation and function. Immune suppression by Treg cells is essential for the maintenance of tolerance and prevention of autoimmunity. Treg dysfunction is a common denominator in autoimmunity an imbalance of Th17/Treg is seen in almost all autoimmune diseases (Hatzioannou et al. 2021) (Fig. 1.2).

Table 1.3 Immunosuppressive cytokines

Cytokine	Function
IL-10	Resolution of inflammation; Inhibition of Th1 inflammatory cytokine synthesis; Inhibition of activated macrophages and dendritic cells.
TGF-β	Resolution of inflammation, limit production of IL-2, INF-γ and TNF-α; Inhibition of proliferation/activation of B cells, T cells and macrophages
IL-35	Block the development of Th1 and Th17 response

1.5 Conclusion

The microbiota plays a critical role in the development, function, and regulation of the immune system, the interaction among both determines the balance between homeostasis and disease. The evidence shows that the microbiome plays a critical role in the training and development of the host's innate and adaptative immune system, and the immune system coordinates the features of host microbiota and dysbiosis is involved in the autoimmunity development.

Dysbiosis might be caused by impaired mucosal barrier, microbial translocation, cross-reactivity of microbial peptides with autoantigens, dysregulation of the immune response; not much is known about the mechanisms of it, but it has been possible to identify certain members of the microbiota that regulate, balance or unbalance the immune response. Changes in the microbial species will affect the balance of Treg and Th17 cells at the mucosa, which modify the homeostasis of the immune response. There are still many questions to solve to understand the balance between microbiota and the immune system, but it is important to know how some bacterial like *B. Fragilis* can promote TH17 response and other strains can induce Treg via its capsular polysaccharide A.

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The Vaccines Induced Autoimmunity

2

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Abstract

Vaccines for the past 300 years have played a crucial role in curbing infectious diseases. The development of effective and safe vaccines has significantly reduced morbidity and mortality caused by infectious diseases. Moreover, recent advancements in vaccinology, immunology, microbiology, and genetic engineering have led to novel advancement in vaccine development. This advancement has been quite evident in the current COVID-19 pandemic, where the swift development and approval of vaccines has stopped the spread of SARS-CoV-2 infection. Additionally, the COVID-19 vaccine has saved patients from severe complications and even death. Despite vaccines' recent advancements and advantages, it would be naïve to believe that vaccines cannot cause adverse reactions. Moreover, evidence suggests vaccines' involvement in developing inflammatory and autoimmune conditions through molecular mimicry, bystander activation, and cross-reactivity. Additionally, the adjuvants and preservatives added in the vaccine formulations may trigger an autoimmune response. As vaccines are administered to healthy individuals, in many cases to children, any adverse complications can have serious consequences. This chapter mainly focuses on mechanisms of vaccine induced autoimmunity, different vaccines reported for such autoimmune conditions, so that the existing knowledge could help in developing safe and effective vaccines.

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2.1 Introduction

Vaccines have been used for the past 300 years, as they are a crucial prophylactic measure for the fight against infectious diseases (Plotkin 2014). Vaccines develop a long-lasting immune response against pathogens, protecting against the pathogens subsequent encounter (Pollard and Bijker 2021). They have played a critical role in eradicating the lethal smallpox virus worldwide and eliminating poliomyelitis and measles virus in most countries (Riedel 2005). The importance of vaccines has been highlighted recently during the coronavirus disease 2019 (COVID-19) pandemic, as the swift development of vaccines has played a crucial role in managing and reducing the disease burden of COVID-19 (Kyriakidis et al. 2021).

Despite their advantages, a growing group of people thinks they endanger one's health instead of protecting from the disease (Aw et al. 2021). This has led to reduced vaccine coverage, evidenced by the increase in recent measles incidence in several countries (Rana et al. 2021). Moreover, the temporal associations of vaccines and disease development make it difficult to deny the justification for vaccine hesitancy (Principi and Esposito 2020). Additionally, reports of adverse reactions after COVID-19 vaccines have further increased the hesitation towards vaccination (Shimabukuro and Nair 2021). During the vaccine administration, safety is a paramount consideration as it is given to healthy individuals.

Although vaccines hedge against infectious diseases, it would be naïve to believe that they don't have any side effects (Pollard and Bijker 2021). Like every other drug, vaccines may have side effects (Shimabukuro and Nair 2021). As every individual is different with respect to their genetic makeup, immune response, and epigenetic factors; therefore, vaccines may have varying reactions in different individuals (Pollard and Bijker 2021). The most severe and peculiar reaction is autoimmunity, where the body's immune response harms itself (Segal and Shoenfeld 2018). Additionally, vaccines formulations have adjuvants that enhance immune response; however, studies have suggested they can develop autoimmune reactions (Agmon-Levin et al. 2009a).

Additionally, the killed/attenuated bacterial or viral components, diluents, residual culture media, preservatives, and adjuvants in the vaccine's formulations can develop autoimmunity through various mechanisms such as molecular mimicry, epitope spreading, cross-reactivity, polyclonal activation (Cohen and Shoenfeld 1996; Agmon-Levin et al. 2009a; Segal and Shoenfeld 2018). As vaccines are administered to healthy individuals and most vaccines are administered to children, the concerns regarding vaccine safety increase. Therefore, this chapter mainly focuses on mechanisms of vaccine induced autoimmunity, different vaccines

reported for such autoimmune conditions, so that the existing knowledge could help in developing safe and effective vaccines.

2.2 Vaccines

Vaccines are biological products that exploit the host's immune system's ability to memorize pathogen encounters; they enable the host immune system to elicit a robust immune response on subsequent encounters (Pollard and Bijker 2021). Variolation, the early version of the now-called vaccines, is believed to have been discovered against deadly smallpox in Asia (Riedel 2005). In 1796, Edward Jenner, the father of vaccinology, demonstrated cowpox virus treatment could prevent smallpox disease (Riedel 2005). Jenner injected an 8-year-old boy with pus taken from a cowpox sore; the little boy had a mild illness and antigen from the cowpox sore, trained the boy's immune system against smallpox, and protected against subsequent infection with smallpox (Riedel 2005). Jenner's discovery led to the development of modern smallpox vaccines that eradicated the smallpox virus from the world (Riedel 2005).

Scientists then began to grow and develop vaccines in the laboratory. Louis Pasteur's experiments spearheaded the development of vaccines as he developed live attenuated cholera vaccine and killed anthrax vaccine (Plotkin 2014). Later vaccine development led to plague vaccine, Bacillus-Calmette-Guerin (BCG) vaccination, pertussis vaccine, tetanus toxoids (Plotkin 2014). Furthermore, the groundbreaking advancement in vaccinology has led to the development of the polio vaccine (Plotkin 2014). The development and research have allowed researchers to combat common and sometimes deadly childhood diseases like measles, mumps, and rubella (MMR) (White et al. 2012). Furthermore, the decades of vaccine research and advancement in immunology, microbiology, molecular genetics, genomics, and new vaccine delivery strategies have led to the development of the lightning-fast COVID-19 vaccines (Kyriakidis et al. 2021).

2.2.1 How Do Vaccines Work?

When foreign microbes invade the human body, the immune system triggers the innate immune response in an attempt to identify, trap, and get rid of this pathogen from our body (Janeway et al. 2001). The signs of this response include inflammation, fever, sneezing, coughing, etc. (Janeway et al. 2001). These innate immune responses then include dendritic cells (DCs) that phagocytise the pathogens and present their antigen to lymphocytes, activating the adaptive immune response (Janeway et al. 2001). The adaptive immune response comprises B cells and T cells that fight such pathogens; they also create a memory against such pathogens, which helps to produce a robust immune response upon subsequent infections with the same pathogen (Janeway et al. 2001). However, obtaining such a natural immunity can sometimes be dangerous, if the pathogen is highly virulent or the

host immune system is too weak to combat the pathogen. Therefore, using the same principles that the body's immune system uses to protect itself, vaccines are developed to trigger the body's adaptive immune system without exposing the host to the full-strength disease (Pollard and Bijker 2021). Vaccines involve using either a live attenuated strain of the pathogen or a killed pathogen, against which the body develops immune response and memory cells that protect the host against subsequent infections (Riedel 2005). Thus, vaccines provoke a natural immune response in the body, making the host immune against dangerous infectious diseases (Pollard and Bijker 2021).

2.2.2 Types of Vaccines

The vaccines can be divided into live attenuated, inactivated, subunit and conjugated, virus-like particles, viral vector, nucleic acid, and toxoids (Plotkin 2014) (Fig. 2.1). The below sections briefly mention about the different types of vaccines with examples.

2.2.2.1 Live Attenuated Vaccine

A live attenuated vaccine uses viable pathogens, i.e., viruses or bacterium, as an antigen to elicit an immune response (Plotkin 2014). The pathogens are generally altered, so they are less virulent or attenuated (Plotkin 2014). The live attenuated vaccine produces a superior immune response as it mimics the natural course of infection (Minor 2015). It stimulates both the humoral and cell-mediated immune

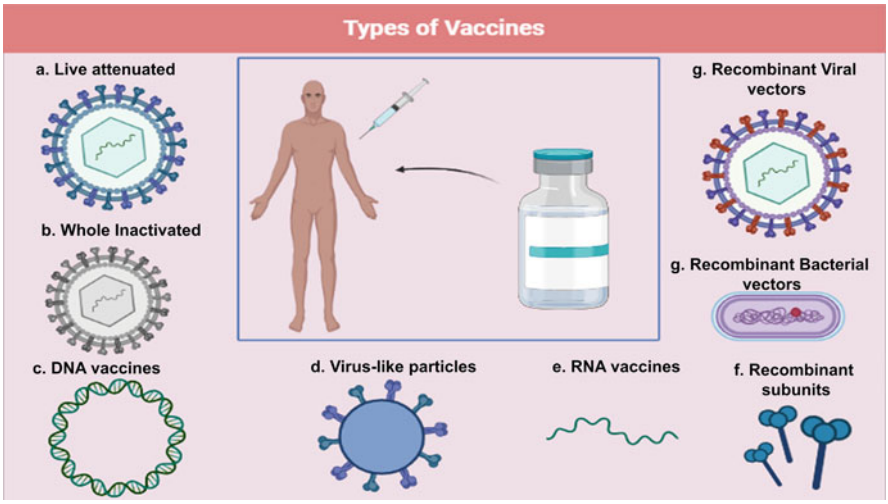

Fig. 2.1 Types of vaccines: (**a**) Live attenuated vaccine, (**b**) Whole inactivated vaccine, (**c**) DNA vaccines, (**d**) Virus-like particles, (**e**) RNA vaccines, (**f**) Subunit vaccine, (**g**) Bacterial vector vaccine, (**h**) Viral vector vaccine

response, thus developing a lifelong immunity with just one or two doses (Minor 2015). The wild-type viruses are attenuated by repeated passages in cell cultures, chick embryos, or different hosts, which introduces mutations in the virus, thus rendering inefficient viral replication when presented as a vaccine (Plotkin 2014). Thus, the immune system recognizes the pathogens and produces a long-lasting immune response that triggers a stronger immune response upon encountering a wild-type virus (Plotkin 2014). However, since a live pathogen is used; therefore, there is always a potential threat exists that the pathogen can revert and be pathogenic to the host (Minor 2015). Thus, there becomes a potential for transmission of disease from the vaccine itself. For example, the rate of reversion of the Polio-Sabin vaccine (OPV) leading to subsequent paralytic disease is about one case in 2.4 million doses of vaccine. A small percentage of recipients of the measles vaccine develop post-vaccine encephalitis or other complications. Some live attenuated vaccines include MMR vaccine, rotavirus vaccine, smallpox vaccine, chickenpox vaccine, yellow fever vaccine, tuberculosis vaccine, typhoid vaccine, Polio-Sabin vaccine (Minor 2015).

2.2.2.2 Inactivated Vaccine

An alternate to live attenuated vaccines are inactivated vaccines or killed vaccines. As the name suggests, it consists of the killed or inactivated virus or bacteria (Plotkin 2014). The bacteria or virus are generally grown in a laboratory and inactivated or killed using heat treatment or chemicals such as formaldehyde or formalin (Sanders et al. 2014). However, the structure of epitopes on surface antigens must be retained during inactivation. Inactivated vaccines are generally considered safe in comparison to live attenuated vaccines as the pathogen's ability to replicate is destroyed, which avoid any chances of reverting to the virulent type; the whole killed pathogen is intact and injected into the host. However, they provide short-term immunity and generally require boosters to ensure long-term immunity (Sanders et al. 2014). Moreover, the adjuvants and additives used in the formulations may lead to allergic or autoimmune reactions (Sanders et al. 2014). Inactivated vaccines are also associated with certain risks when inactivation is not successful. For example, a serious complication with the first Salk vaccines arose when formaldehyde failed to kill all viruses in two vaccine lots, which caused paralytic polio in a high percentage of recipients. Examples of killed vaccines include Polio-Salk vaccine, influenza vaccine, hepatitis A vaccine, rabies vaccine, rubella vaccine, anthrax vaccine, cholera vaccine, pertussis vaccine, SARS-CoV-2 vaccine, and plague vaccine (Plotkin 2014; Sapkal et al. 2021; Ella et al. 2021; Al Kaabi et al. 2021).

2.2.2.3 Subunit and Conjugate Vaccines

The subunit and conjugate vaccines only comprise the antigenic part of the pathogen (Plotkin 2014). Therefore, the host immune system produces an immune response against the specific protein of the pathogen (Wang et al. 2020). The subunit vaccines are produced by growing the pathogens in vitro and by isolating the particular proteins required to elicit the immune response (Wang et al. 2020). Alternatively,

the subunit vaccines can be prepared by genetic engineering (Plotkin 2014). Here, the gene encoding the protein can be inserted and expressed into another virus, bacteria, or cell lines, leading to efficient production of the subunit or conjugate vaccines (Wang et al. 2020). However, limitations of these vaccines are that they may require booster doses and adjuvants for longer protection against pathogens and inadequate cellular immunity is generated (Wang et al. 2020). Nevertheless, T helper cells can be activated by conjugating polysaccharide antigen to some sort of protein carrier. For example, the vaccine for *Haemophilus influenzae* type b (Hib; causing bacterial meningitis), consists of type b capsular polysaccharide covalently linked to a protein carrier, tetanus toxoid. Examples of subunit vaccines include the hepatitis B vaccine, influenza vaccine, pertussis vaccine, diphtheria vaccine, tetanus vaccine, pertussis vaccine, pneumococcal vaccine, meningococcal vaccine, and human papillomavirus vaccine (Wang et al. 2020).

2.2.2.4 Virus Like Particles

The virus like particles (VLP) vaccine is genetically engineered. VLPs are virus-derived structures that mimic the virus but lack the wild-type virus's genetic material (Nooraei et al. 2021). The expression and assembly of the VLPs are generally grown in cell-free systems (Nooraei et al. 2021). The VLPs are gaining popularity as they produce a prompt immune response because of the size and shape of VLPs, which are similar to the wild-type virus (Plotkin 2014). Moreover, they are considered safe as they do not contain the genetic material of the virus (Plotkin 2014). Example of VLPs is the human papillomavirus (HPV) vaccine, hepatitis B vaccine, influenza vaccine, hepatitis E vaccine (Nooraei et al. 2021). Recently, Covifenz vaccine—a plant-based vaccine for SARS-CoV-2 has been developed by Medicago and GlaxoSmithKline (GSK) in Canada. Covifenz uses Coronavirus-Like Particle (CoVLP) technology with the vaccine composed of recombinant spike (S) glycoprotein expressed as virus-like particles (VLPs) co-administered with GSK's pandemic adjuvant. This vaccine is refrigerator-stable (Arthur 2022).

2.2.2.5 Viral Vector Vaccines

Viral vector vaccines utilize a viral vector to deliver the vaccine. The advantage of using viral vectors is that they can elicit a natural immune response without adjuvants (Ura et al. 2014). Some examples of several viral vectors used are adenovirus, adeno-associated viruses, measles virus, influenza virus, vesicular stomatitis virus, rotavirus, lentivirus, vaccinia virus, cytomegalovirus, and sendai virus (Ura et al. 2014). The advantages of viral vector vaccines are specific delivery of genes, efficient gene transduction, and induction of robust immune response. Examples of viral vector vaccines include Ebola, Zika, influenza, and human immunodeficiency virus (HIV) vaccines (Ura et al. 2014). Moreover, a recent COVID-19 vaccine has been developed by AstraZeneca with the recombinant adenovirus vector (ChAdOx1) (Folegatti et al. 2020).

2.2.2.6 Nucleic Acid Vaccine

Nucleic acid vaccines are relatively new technology, which has high efficiency and low cost (Qin et al. 2021). They include DNA and mRNA-based vaccines. For DNA vaccines, after internalization, DNA is transferred into the nucleus and translated into the cytoplasm (Hobernik and Bros 2018). In comparison, mRNA vaccines carry the antigen coding mRNA, which are delivered to the antigen presenting cells (APCs) and translated into the cytoplasm (Pardi et al. 2018). The expressed proteins are presented by MHC class I on the APCs, activating the $CD8^+$ T cells immune response (Hobernik and Bros 2018). The advantage of nucleic acid vaccines include that they are non-infectious; they only target the specific antigen (Qin et al. 2021). Moreover, they induce both innate and adaptive immune responses (Qin et al. 2021). The recent COVID-19 vaccines by Pfizer-BioNTech and Moderna have been developed on the mRNA vaccines platform (Polack et al. 2020; Baden et al. 2020). Furthermore, a DNA vaccine encoding the S protein of SARS-CoV was found to induce T cells, a neutralizing antibody response, and protective immunity (Prompetchara et al. 2021). OncoSec's CORVax12, a trial vaccine against SARS-CoV-2 involves the co-administration of TAVO™ (plasmid IL-12) with a DNA-encodable variety of the SARS-CoV-2 S glycoprotein to increase the immunogenicity (Providence Health and Services 2022, NCT04627675).

2.2.2.7 Toxoids

Inactivated exotoxins are referred to as "toxoids." Some bacterial infections can cause pathogenesis through the exotoxin produced by the bacterium (Clem 2011). These toxins can be inactivated by the use of heat treatment or chemicals like formalin (Clem 2011). Diphtheria and tetanus vaccines, for example, can be made by purifying the bacterial exotoxin and then inactivating the toxin with formaldehyde to form a toxoid (Choi et al. 2018). Vaccination with the toxoid induces anti-toxoid antibodies, which are also capable of binding to the toxin and neutralizing its effects (Choi et al. 2018).

2.3 Autoimmune Diseases

Autoimmune diseases are characterized by an aberrant immune response against the host's own body, wherein the immune system loses tolerance and recognizes the body's tissue as non-self (Wang et al. 2015). The prevalence of autoimmune diseases ranges from 3% to 5% worldwide (Leslie and Hawa 1994; Wang et al. 2015). Autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes mellitus (T1DM) have profound implications and significantly affect mortality and morbidity (Wang et al. 2015). Autoimmune diseases affect patients of any age, gender, and ethnicity (Wang et al. 2015). Moreover, despite enormous research, the exact etiology of autoimmune diseases is unclear. Several factors like genetics, epigenetics, stress, environmental factors may trigger the development of autoimmune diseases (Costenbader et al. 2012). Additionally, there is no cure for most autoimmune

diseases, and treatment options mainly focus on symptomatic relief (Chandrashekara 2012).

Multiple factors confer the risk of developing autoimmune diseases; it is challenging to pinpoint the exact trigger for autoimmune diseases (Costenbader et al. 2012). Several factors, including environment, nutrition, stress, microbiota, infections, tobacco smoke, pharmaceutical agents, hormones, ultraviolet, light, silica solvents, heavy metals, vaccines, and collagen/silicone implants, can trigger the development of autoimmune diseases (Shoenfeld et al. 2000; Costenbader et al. 2012). Genetic association studies have suggested the association of major histocompatibility complex (MHC) with susceptibility to autoimmune diseases (Matzaraki et al. 2017). Additionally, studies have highlighted the association of genetic variants of the HLA DRB1 gene with various autoimmune diseases (Arango et al. 2017). Moreover, previous studies have found the involvement of immune system-associated genes such as *forkhead boxp3 (FOXP3)*, *interferon-gamma (IFNG)*, *interleukin 4 (IL4)*, *proteasome 20S subunit beta 8 (PSMB8)*, *NLR family pyrin domain containing 1 (NLRP1)*, *neuropeptide Y (NPY)*, and *interleukin-1-beta (IL1B)* with susceptibility to the development of autoimmune diseases (Dwivedi et al. 2013b; Owen et al. 2006; Pontillo et al. 2010; Imran et al. 2012; Laddha et al. 2014; Jadeja et al. 2017; Wang et al. 2017; Wu et al. 2021; Giri et al. 2021).

Although the exact triggering factor is unknown, the initial trigger activates an innate immune response against self-antigens (Arango et al. 2013). The underlying mechanisms such as molecular mimicry, epitope spreading, cross-reactivity, polyclonal activation triggers the innate immune response against self-antigens (Arango et al. 2013). The activated innate immune response leads to the overproduction of inflammatory cytokines and eventually activates the adaptive immune response (Wang et al. 2015). The adaptive immune response comprises B and T cells, and autoreactive B and T cells are the hallmark of the autoimmune reaction (Wang et al. 2015). Autoreactive B cells produce autoantibodies found in patients with various autoimmune diseases like RA, MS, SLE, and T1DM (Hampe 2012). The autoantibodies are directed against functional structures of cells like cellular receptors (Elkon and Casali 2008). These antibodies establish their pathogenic effects by binding to cell surfaces, triggering cell lysis and tissue damage through complement activation and antibody-dependent cellular toxicity (Hampe 2012). Moreover, these autoantibodies play a crucial role in the diagnosis and classification of autoimmune diseases (Elkon and Casali 2008).

Apart from autoantibodies and autoreactive B and T cells have been observed in patients with autoimmune diseases (Skapenko et al. 2005). The autoreactive T cells circulate throughout the body; however, their presence is higher at the site of the target organ (Boehncke and Brembilla 2019). These cytotoxic T cells detect the specific tissue by binding the T cell receptor on $CD8^+$ T cells to the autoantigen presented by the MHC class I molecule (Skapenko et al. 2005). The CTLs then mediate their cytotoxic function by (1) releasing cytotoxic granules (Granzyme B and perforin), resulting in the apoptosis of target cells, (2) FAS-FASL mediated target cell lysis, (3) pro-inflammatory cytokines (TNF-α and IFN-γ), which exacerbate the tissue damage. A subset of CTLs called the tissue-resident memory (TRM)

T cells resides in the particular tissue and exerts their autoimmune response (Dornmair et al. 2003).

Other than $CD8^+$ T cells, the other subset of autoreactive T cells in $CD4^+$ T cells has been observed in various autoimmune diseases (Dornmair et al. 2003). These autoreactive $CD4^+$ T cells are considered to be the drivers of the autoimmune response (Raphael et al. 2020). Although their exact role in autoimmune diseases is unclear, once activated, they are known to aid the stimulation of APCs by binding CD40 to CD40L (Harding and Allison 1993; Elgueta et al. 2009). Moreover, the binding of CD28 and B7 further aids the activation of CTLs, which exacerbates the autoimmune response (Harding and Allison 1993; Elgueta et al. 2009). Additionally, they also mediate FAS-FASL-mediated apoptosis (Tateyama et al. 2000). Furthermore, they secrete key pro-inflammatory cytokines like IFN-γ, IL-1, TNF-α, and IL-17, contributing to the inflammatory response in various autoimmune diseases (Tesmer et al. 2008).

Another subset of $CD4^+$ T cells is the regulatory T cells (Tregs), which are known to maintain peripheral tolerance by controlling such aberrant autoimmune responses by self-reactive T and B cells (Dwivedi et al. 2013a, 2015a). However, previous studies have reported qualitative and quantitate defects in Tregs in various autoimmune diseases (Long and Buckner 2011; Dwivedi et al. 2013c; Giri et al. 2020a, b). Moreover, an imbalance in $CD8^+$ T cells and Tregs is observed in autoimmune disease such as vitiligo, as the $CD4^+/CD8^+$ T cell ratio is reduced in these patients (Dwivedi et al. 2013a, 2015a). Overall, these studies suggest multiple triggering factors like infections, genetics, stress, environment, epigenetics, vaccines can lead to innate immune system activation (Wang et al. 2015), which leads to widespread activation of $CD4^+$ T cells, $CD8^+$ T cells, and B cells (Giri et al. 2020b). Moreover, it has been suggested that the qualitative and quantitative defects in Tregs contribute to the pathogenesis of autoimmune diseases such as vitiligo (Dwivedi et al. 2016). The below sections briefly introduce different types of autoimmune diseases.

2.3.1 Types of Autoimmune Disease

Based on the site of the autoimmune response, the disorder is classified into systemic autoimmune diseases and organ-specific autoimmune diseases (Zeher and Szegedi 2007). Here, we discuss systemic and organ-specific autoimmune diseases.

2.3.1.1 Systemic Autoimmune Disease

Systemic autoimmune diseases are generalized that target multiple organs or tissues throughout the body (Shi et al. 2013). Examples of systemic autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, ankylosing sponkylitis, scleroderma, and Sjogren's syndrome. These diseases reflect a general defect in immune regulation that results in hyperactive T cells and B cells. Tissue damage is widespread, both from cell-mediated immune responses and from direct cellular damage caused by autoantibodies or by accumulation of immune complexes.

2.3.1.1.1 Rheumatoid Arthritis (RA)

RA is a chronic autoimmune disorder characterized by inflammation in joints, synovial membrane contributing to bone and cartilage damage, resulting in disability, discomfort, stiffness, and decreased life expectancy (Carbone et al. 2020). Most often, RA occurs in women from 40 to 60 years old. The major symptom is chronic inflammation of the joints, although the hematologic, cardiovascular, and respiratory systems are also frequently affected. The exact etiology of RA is unknown; however, genetics, environment, and other factors like birth weight, diet, alcohol, and smoking are extensively involved in the risk of developing RA (Deane et al. 2017). Studies have suggested the role of both innate and adaptive immune responses in joint destruction (Firestein and McInnes 2017). After the initial trigger, innate immune cells get activated, resulting in specific B and T cell activation in RA patients (Firestein and McInnes 2017). Many individuals with rheumatoid arthritis produce a group of autoantibodies called rheumatoid factors that are reactive with determinants in the Fc region of IgG (Firestein and McInnes 2017). The classic rheumatoid factor is an IgM antibody with that reactivity. Such autoantibodies bind to normal circulating IgG, forming IgM-IgG complexes that are deposited in the joints. These immune complexes can activate the complement cascade, resulting in a type III hypersensitive reaction, which leads to chronic inflammation of the joints. Additionally, persistent inflammation leads to complex systemic manifestations resulting in rheumatoid lung carditis vasculitis, anemia, atherosclerosis, myocardial disease, lymphoma, and osteoporosis (Anić and Mayer 2014).

2.3.1.1.2 Systemic Lupus Erythematosus

SLE is an inflammatory condition characterized by systemic autoimmune damage of kidneys, skin, liver, lungs, heart, and brain (de Oliveira 2018). It is a heterogeneous systemic condition damaging multiple organs and tissues, resulting in clinical features involving fever, arthritis, renal disorder, hematological disorder, and cardiovascular disease (Cojocaru et al. 2011). Genetic and environmental factors are involved in the etiology of SLE (Kamen 2014). SLE's pathogenesis suggests TLR mediated IFN-α production activates innate immune cells like dendritic cells (DCs) (Rönnblom and Pascual 2008). DCs further activate autoreactive T and B cells leading to increased production of autoantibodies. Affected individuals may produce autoantibodies to a vast array of tissue antigens, such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors; interaction of these autoantibodies with their specific antigens produces various symptoms. Autoantibody specific for RBCs and platelets, for example, can lead to complement-mediated lysis, resulting in hemolytic anemia and thrombocytopenia, respectively. When immune complexes of autoantibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitive reaction develops. The complexes activate the complement system and generate membrane-attack complexes and complement split products that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis. $CD4^+$ T cells produce pro-inflammatory cytokines like IL-23 and IL-6, resulting in SLE pathogenesis (Moulton et al.

2017). Although treatment has dramatically improved SLE outcomes, patients still suffer from significant morbidity (Maidhof and Hilas 2012).

2.3.1.1.3 Multiple Sclerosis

MS is an autoimmune, chronic, inflammatory, demyelinating, and neurological disorder that affects the central nervous system (CNS) (Polman et al. 2011). The infiltration of immune cells across the blood–brain barrier is the hallmark of MS (Matute-Blanch et al. 2017). Individuals with this disease produce autoreactive T cells that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers. The cerebrospinal fluid of patients with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin. Since myelin functions to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions. Mainly, activated macrophages, autoantibodies, $CD8^+$ T cells, $CD4^+$ T cells, and B cells are detected in MS patients (van Langelaar et al. 2020). These immune cells mediate inflammation, demyelination, and neuron degradation (van Langelaar et al. 2020). The autoimmune response against myelin sheath results in depression, vision loss, muscle weakness, and cognitive defects (Matute-Blanch et al. 2017).

2.3.1.1.4 Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a type of spondyloarthropathy, which causes chronic inflammation in spine joints (Garcia-Montoya et al. 2018; Zhu et al. 2019). It causes severe chronic pain and in advance cases results in spine fusion (Zhu et al. 2019). The complex interaction between genetic background and environment are considered to be responsible for the etiology of AS (Zhu et al. 2019). The pathogenesis of AS is unknown; however, cytokines such IL-23, IL-27, and human leukocyte antigen (HLA)-B27 are suggested to be responsible in the pathogenesis of AS (Zhu et al. 2019). The current treatment options include tumor necrosis factor (TNF) inhibitors, disease-modifying anti-rheumatic drugs (bDMARDs) and IL-17 blockers (Garcia-Montoya et al. 2018).

2.3.1.1.5 Scleroderma

Scleroderma is a chronic autoimmune connective tissue disorder; it causes hardening and thickening of skin and tissues (Odonwodo et al. 2021). The exact etiology of scleroderma is unknown but genetics and environmental factors play a role in pathogenesis of scleroderma (Odonwodo et al. 2021). Silica and some organic solvents are risk factors for scleroderma, which causes activation of immune system, damaging the blood vessels and tissues (Odonwodo et al. 2021). Current treatment options aim to relieve symptoms and slow disease progression (Odonwodo et al. 2021).

2.3.1.1.6 Sjogren's Syndrome

Sjogren's syndrome is a systemic autoimmune disorder, characterized by dry eye and mouth due to inflammation in lacrimal and salivary glands (Carsons and Patel

2021). It causes extra-glandular involvement in organs like joints, skin, lungs, gastrointestinal (GI) tract, nervous system, and kidneys (Carsons and Patel 2021). The exact etiology is unknown; however, individuals sharing haplotypes in the HLA-DQA_DQB haplotypes are at risk of developing Sjogren's syndrome (Carsons and Patel 2021). Management of Sjogren's syndrome is done by replacing moisture at affected glandular sites and diminishing the autoimmune response locally as well as systemically (Carsons and Patel 2021).

2.3.1.2 Organ-Specific Autoimmune Diseases

As the name suggests, organ-specific autoimmune diseases are those which target a specific organ or tissue (Zeher and Szegedi 2007). Examples of organ-specific autoimmune diseases include Insulin-Dependent Diabetes Mellitus (IDDM or T1DM), Hashimoto's thyroiditis, vitiligo, Graves' disease, autoimmune anemia, Goodpasture's Syndrome and myasthenia gravis.

2.3.1.2.1 Type-1 Diabetes Mellitus (T1DM)

T1DM is a chronic disease characterized by the autoimmune loss of the pancreatic Beta cells (β)-cells that secrete insulin (Hara et al. 2013). The etiology of T1D is unclear; however, genetic and environmental factors trigger the most common factors (Hara et al. 2013). The pathogenesis of T1D is characterized by insulitis, elevated autoantibody production against β-cell antigens, followed by reduced insulin secretion and β-cell death (Pihoker et al. 2005). The abnormalities in glucose metabolism that are caused by the destruction of islet beta cells result in serious metabolic problems that include ketoacidosis and increased urine production. The destruction of β-cells may occur over the years; however, extreme symptoms like hyperglycemia, thirst, urination, loss of appetite, fatigue usually are diagnosed after all the β-cells are destroyed (Pihoker et al. 2005). The late stages of the disease are often characterized by atherosclerotic vascular lesions, which in turn cause gangrene of the extremities due to impeded vascular flow, renal failure, and blindness.

2.3.1.2.2 Hashimoto's Thyroiditis

Hashimoto's thyroiditis, also called chronic lymphocytic thyroiditis, is characterized by autoimmune destruction of thyroid cells (Fröhlich and Wahl 2017). The exact etiology is poorly understood; however, most patients develop autoantibodies against thyroid antigens (Fröhlich and Wahl 2017). These antigens mainly include thyroid proteins, such as thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine (Fröhlich and Wahl 2017). Binding of the autoantibodies to these proteins interferes with iodine uptake and leads to decreased production of thyroid hormones (hypothyroidism). Infiltration of lymphocytes and fibrosis are the critical features of autoimmune Hashimoto thyroiditis (Rydzewska et al. 2018). These autoantibodies mediate the lysis of thyrocytes through complement fixation and antibody-dependent cellular toxicity (Fröhlich and Wahl 2017).

2.3.1.2.3 Vitiligo

Vitiligo is a complex autoimmune skin depigmenting disease characterized by loss of function melanocytes mainly by the action of melanocyte specific cytotoxic T cells (Bergqvist and Ezzedine 2020). Several factors, including infections, genetics, oxidative stress, altered melanocyte adhesion, trauma, trigger vitiligo pathogenesis (Dwivedi et al. 2015a; Rashighi and Harris 2017; Jadeja et al. 2021). The initial trigger activates the innate immune response, resulting in a widespread activation of self-reactive $CD4^+$ T cells, $CD8^+$ T cells, and B cells response (Strassner and Harris 2016; El-Gayyar et al. 2020; Giri et al. 2020b). Furthermore, anti-melanocyte specific antibodies found in vitiligo patients are positively correlated with disease activity (Dwivedi et al. 2015b; El-Gayyar et al. 2020). Additionally, the altered Treg cells number and suppressive function lead to unchecked proliferation of these self-reactive $CD4^+$ T cells, $CD8^+$ T cells, and B cells (Dwivedi et al. 2013a, 2015b; Giri et al. 2020b), contributing to melanocytes destruction leading to vitiligo pathogenesis.

2.3.1.2.4 Graves' Disease

Graves' disease (GD) is one of the most common autoimmune thyroid diseases (Rydzewska et al. 2018). The pathogenesis of the disease is characterized by production of IgG autoantibodies against thyrotropin receptor (Rees Smith et al. 1988). Patients with Graves' disease produce autoantibodies that bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones. Thus, binding of the autoantibodies causes an autonomous and over production of thyroid hormones. The symptoms of Graves' disease include heat intolerance, weight loss, rapid and irregular heartbeat, goitre (Rydzewska et al. 2018).

2.3.1.2.5 Autoimmune Anemia

Autoimmune anemia mainly include pernicious anemia, autoimmune hemolytic anemia, and drug-induced hemolytic anemia (Silberstein 2007; Garratty 2009; Rodriguez and Shackelford 2021). Pernicious anemia is caused by autoantibodies to intrinsic factor, a membrane-bound intestinal protein on gastric parietal cells (Rodriguez and Shackelford 2021). Intrinsic factor facilitates uptake of vitamin B12 from the small intestine. Binding of the autoantibody to intrinsic factor blocks the intrinsic factor-mediated absorption of vitamin B12 (Rodriguez and Shackelford 2021). In the absence of sufficient vitamin B12, which is necessary for proper hematopoiesis, the number of functional mature red blood cells decreases below normal (Rodriguez and Shackelford 2021). Pernicious anemia is treated with injections of vitamin B12, thus circumventing the defect in its absorption (Rodriguez and Shackelford 2021). Patients individual with autoimmune hemolytic anemia produce autoantibody to RBC antigens, triggering complement-mediated lysis or antibody-mediated opsonization and phagocytosis of the red blood cells (Silberstein 2007). One form of autoimmune anemia is drug-induced (Garratty 2009). For example, when certain drugs such as penicillin or the anti-hypertensive agent methyldopa interact with red blood cells, the cells become antigenic (Garratty 2009).

2.3.1.2.6 Goodpasture's Syndrome

Goodpasture's syndrome (GS) is mediated by binding of autoantibodies specific for certain basement-membrane antigens to the basement membranes of the kidney glomeruli and the alveoli of the lungs (DeVrieze and Hurley 2021). Subsequent complement activation leads to direct cellular damage and an ensuing inflammatory response mediated by a buildup of complement split products (DeVrieze and Hurley 2021). Further damage to the glomerular and alveolar basement membranes leads to progressive kidney damage and pulmonary hemorrhage. Death may ensue within several months of the onset of symptoms (DeVrieze and Hurley 2021).

2.3.1.2.7 Myasthenia Gravis

Myasthenia gravis (MG) is mediated by blocking antibodies. Patients with MG produces autoantibodies that bind the acetylcholine receptors on the motor end-plates of muscles, blocking the normal binding of acetylcholine and also inducing complement-mediated lysis of the cells (Jayam Trouth et al. 2012; Koneczny and Herbst 2019). The result is a progressive weakening of the skeletal muscles. Ultimately, the antibodies destroy the cells bearing the receptors (Jayam Trouth et al. 2012; Koneczny and Herbst 2019). The early signs of this disease include drooping eyelids and inability to retract the corners of the mouth, which gives the appearance of snarling (Jayam Trouth et al. 2012; Koneczny and Herbst 2019). Without treatment, progressive weakening of the muscles can lead to severe impairment of eating as well as problems with movement. However, with appropriate treatment, this disease can be managed quite well and afflicted individuals can lead a normal life (Jayam Trouth et al. 2012; Koneczny and Herbst 2019).

2.4 Mechanism of Vaccine Triggered Autoimmunity

Vaccines are an effective preventive measure against pathogenic organisms; however, some vaccines can trigger autoimmune reactions (Cohen and Shoenfeld 1996). Multiple factors such as stress, infections, environment, genetics, and genetics govern the immune response produced by the particular individual (Varadé et al. 2021). It becomes complicated to predict if an individual will develop an autoimmune reaction. Moreover, multiple factors can trigger the development of autoimmune response post-vaccination (Shoenfeld et al. 2000). Additionally, viruses and microorganisms have been suggested as a triggering factor in the development of autoimmunity. Vaccines comprise these live or killed organisms, which can lead to autoimmune reactions through molecular mimicry, cross-reactivity, bystander activation, and epitope spreading (Agmon-Levin et al. 2009a; Arango et al. 2013) (Table 2.1, Fig. 2.2).

Additionally, vaccine formulations comprise adjuvants that are known to enhance immune response (Agmon-Levin et al. 2009a; Israeli et al. 2015), which suggests vaccinations may trigger autoimmune response (Shoenfeld and Aron-Maor 2000; Tishler and Shoenfeld 2004; Agmon-Levin et al. 2014a). Furthermore, adjuvants can

Table 2.1 Potential mechanisms of vaccines induced autoimmunity

Vaccine component	Potential mechanisms	Reference
Adjuvants	Aluminum salts activate DCs, increases inflammation, increases pro-inflammatory cytokine production, and increases chemokine production.	Satoh and Reeves (1994), Satoh et al. (1995), Di Benedetto et al. (2002), Kool et al. (2008), Nancy and Shoenfeld (2008), Agmon-Levin et al. (2009a, 2012, 2014b), Balofsky et al. (2010), Shoenfeld and Agmon-Levin (2011), Rosenblum et al. (2011), Katzav et al. (2012), Zafrir et al. (2012), Cruz-Tapias et al. (2013), Perricone and Shoenfeld (2013), Colafrancesco et al. (2014, 2013), Perricone et al. (2013), Soriano et al. (2014), Tomljenovic et al. (2014), Goren et al. (2014, 2015), Austin et al. (2015), Butnaru and Shoenfeld (2015), Nesher et al. (2015), Israeli et al. (2015), Rodriguez-Pintó and Shoenfeld (2015), Bassi et al. (2015), Guimarães et al. (2015), David et al. (2016), Dagan et al. (2016), Watad et al. (2017a, b, 2018a, b, 2019), Segal et al. (2018), Bragazzi and Hejly (2020), Borba et al. (2020), Halpert et al. (2021), Ruyer-Thompson et al. (2021)
	Mineral oil adjuvant induces chronic inflammatory response	
	Alum hydroxide promotes NLRP inflammasome production	
	Adjuvant promote ASIA symptoms	
	Aluminum salts regulates Th2 response, they suppress Treg number and function	
	Silicone based adjuvant exposure leads to long-term inflammatory conditions resulting in broad spectrum of autoimmune inflammatory syndrome	
Viral antigens	Molecular mimicry and cross-reactivity lead to autoantibody production and $CD4^+$ and $CD8^+$ T cells activation.	Agmon-Levin et al. (2009a), Blank et al. (2013), Arango et al. (2013), Israeli et al. (2015), Smyk et al. (2015), Guimarães et al. (2015)
	Viral antigens may promote ASIA symptoms	
	Viral antigens lead to polyclonal activation of B and T cells, suppression of Tregs, cytokine storm, Viral induced autoantibodies, altered self-antigens, expression of HLA antigens, induction of novel antigens	
mRNA-based viral vaccine	mRNA can bind to pattern recognition receptors, toll-like receptors 3, 7, and 8, and stimulate the innate immune response and production of pro-inflammatory cytokines like IFN-γ.	Wang et al. (2021), Talotta (2021)

suppress Tregs numbers and function (Agmon-Levin et al. 2009a; Israeli et al. 2015). In addition, the host genetic factors may also confer susceptibility to autoimmune response post-vaccination (Agmon-Levin et al. 2009a; Arango et al. 2017). Therefore, the hyperimmune response against these adjuvants may additionally trigger an autoimmune response (Table 2.1, Fig. 2.2).

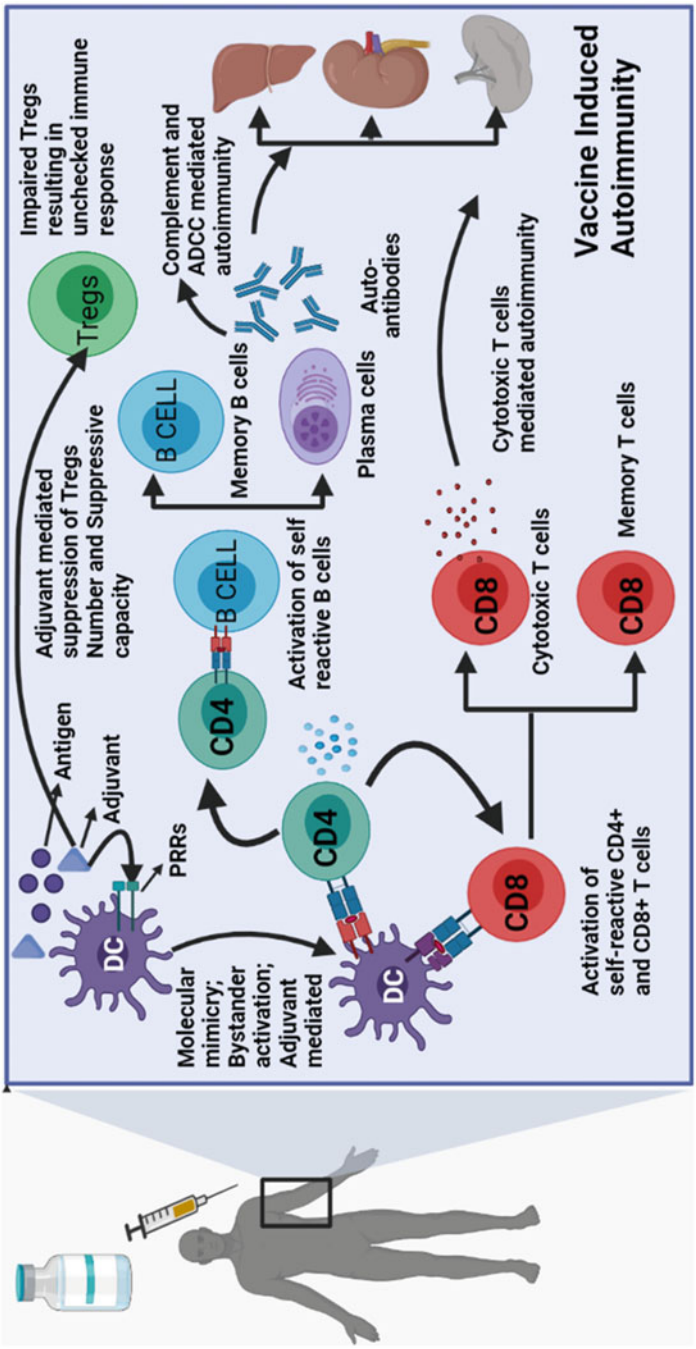

Fig. 2.2 Generation of vaccine induced autoimmunity. Vaccines protect the host from infectious pathogens. However, recent evidence suggests the involvement of vaccines in triggering inflammatory and autoimmune reactions. Multiple factors can trigger the development of autoimmune response post-vaccination. Vaccines comprise live or killed organisms, leading to autoimmune

2.4.1 Adjuvants

Although adjuvants are thought to pose no threats against the host, studies suggest they can trigger an autoimmune response (Cohen and Shoenfeld 1996; Agmon-Levin et al. 2009a; Israeli et al. 2009; Maślińska et al. 2013; Colafrancesco et al. 2014; Guimarães et al. 2015). Adjuvants can trigger an autoimmune response by mechanisms like molecular mimicry, hyperactivation of the immune response, cross-reactivity, and polyclonal activation of cellular and humoral immunity (Israeli et al. 2015) (Table 2.1). The different adjuvants like alum and mineral oils may have varied reactions, leading to different autoimmune responses (Israeli et al. 2015) (Table 2.1). One of the most common adjuvants used with viral vaccines is alum hydroxide (Israeli et al. 2015). Alum hydroxide has been linked with an increased inflammatory response due to increased IL-1 and IL-18 cytokine production by macrophages (Kool et al. 2008; Israeli et al. 2015). Moreover, alum hydroxide promotes NLRP inflammasome production, which can direct the humoral immune response (Kool et al. 2008; Israeli et al. 2015) (Table 2.1). Furthermore, the alum-based adjuvants have been associated with various autoimmune diseases like MS, polymyalgia rheumatica, and Gulf-War syndrome (Gherardi and Authier 2003; Petrik et al. 2007; Israeli et al. 2015).

Silicone oil-based nano-adjuvants and injectable silicone implants are also used as an vaccine delivery vehicle (Lofthouse et al. 2002; Razim et al. 2021). Such implants release low level of antigen over a longer period of time, thus providing sustained antibody levels for longer duration (Lofthouse et al. 2002). However, long-term inflammatory conditions are linked with silicone exposure which results in broad spectrum of autoimmune inflammatory syndrome induced by such adjuvants (Soriano et al. 2014; Goren et al. 2015; Watad et al. 2019; Halpert et al. 2021). Some of the most common complications after silicone implants are chronic fatigue syndrome, ASIA, Non-Hodgkin's lymphoma, Churg-Strauss syndrome, and rheumatic disorders (Nancy and Shoenfeld 2008; Goren et al. 2014; David et al. 2016; Watad et al. 2018b). Additionally, severe ASIA syndrome is found to be associated with lymph node, thoracic, and pulmonary silicone infiltration after breast implants (Nesher et al. 2015).

Another adjuvant is mineral oil, which is considered non-toxic but distributes throughout the body upon injection (Di Benedetto et al. 2002; Bassi et al. 2015;

Fig. 2.2 (continued) reactions through molecular mimicry, cross-reactivity, bystander activation, and epitope spreading. Additionally, vaccine formulations include adjuvants, which lead to increased inflammation and trigger autoimmune reactions. Altogether, these lead to activations of dendritic cells, which activate self-reactive $CD8^+$ T cells, $CD4^+$ T cells and B cells. The autoreactive $CD4^+$ T cells produce pro-inflammatory cytokines and help in the activation of self-reactive $CD8^+$ T cells and B cells. These self-reactive cytotoxic T cells lead to perforin, and granzyme B mediated autoimmunity. Moreover, self-reactive B cells produce autoantibodies which result in complement and ADCC mediated autoimmunity. Furthermore, adjuvants suppress Tregs numbers and function, which are unable to curb these aberrant immune responses. Thus, the activated self-reactive $CD8^+$ T cells, $CD4^+$ T cells, B cells, and impaired Tregs suppressive activity led to autoimmunity

Israeli et al. 2015). The mineral oil induces a chronic inflammatory reaction called sclerosing lipogranuloma (Di Benedetto et al. 2002; Bassi et al. 2015; Israeli et al. 2015). Additionally, pristane and mineral oils adjuvants induce plasmacytomas and lupus-related anti-nRNP/Sm/Su antibodies (Satoh and Reeves 1994; Satoh et al. 1995; Israeli et al. 2015). Interestingly, Shoenfeld and Agmon-Levin suggested that autoimmune/inflammatory syndrome induced by adjuvants (ASIA) also known as Shoenfeld's syndrome, is a combination of five autoimmune reactions, namely the post-vaccination phenomena, the macrophagic myofasciitis syndrome (MMF), the Gulf-War syndrome (GWS), silicosis, and the sick building syndrome (SBS) (Shoenfeld and Agmon-Levin 2011; Watad et al. 2017a) (Table 2.1). Thus, AISA suggests the possible role of adjuvants and vaccines in development of autoimmunity (Agmon-Levin et al. 2012; Katzav et al. 2012; Cruz-Tapias et al. 2013; Perricone et al. 2013; Soriano et al. 2014; Goren et al. 2015; Watad et al. 2017b, 2018a; Borba et al. 2020; Ruyer-Thompson et al. 2021). Cases of ASIA have been observed for vaccines against HPV, HBV, and seasonal influenza, which mainly used aluminum hydroxide as adjuvants (Balofsky et al. 2010; Shoenfeld and Agmon-Levin 2011; Zafrir et al. 2012; Perricone and Shoenfeld 2013; Colafrancesco et al. 2013; Tomljenovic et al. 2014; Austin et al. 2015; Rodriguez-Pintó and Shoenfeld 2015; Guimarães et al. 2015).

The common complication of ASIA are chronic fatigue syndrome, still disease, lymphoma, fibromyalgia Sjögren's syndrome, endocrine autoimmune syndrome (Satoh and Reeves 1994; Satoh et al. 1995; Di Benedetto et al. 2002; Kool et al. 2008; Nancy and Shoenfeld 2008; Agmon-Levin et al. 2009a, 2012, 2014b; Balofsky et al. 2010; Shoenfeld and Agmon-Levin 2011; Rosenblum et al. 2011; Katzav et al. 2012; Zafrir et al. 2012; Cruz-Tapias et al. 2013; Perricone and Shoenfeld 2013; Colafrancesco et al. 2014, 2013; Perricone et al. 2013; Soriano et al. 2014; Tomljenovic et al. 2014; Goren et al. 2014, 2015; Austin et al. 2015; Butnaru and Shoenfeld 2015; Nesher et al. 2015; Israeli et al. 2015; Rodriguez-Pintó and Shoenfeld 2015; Bassi et al. 2015; Guimarães et al. 2015; David et al. 2016; Dagan et al. 2016; Watad et al. 2017a, b, 2018a, b, 2019; Segal et al. 2018; Bragazzi and Hejly 2020; Borba et al. 2020; Halpert et al. 2021; Ruyer-Thompson et al. 2021). Moreover, the HPV vaccine has been related to autoimmune reactions such as SLE, Guillain-Barre syndrome (GBS), idiopathic thrombocytopenia (ITP) (Smyk et al. 2015). Additionally, Hashimoto's thyroiditis, Graves' disease, T1DM can be triggered by adjuvants (Guimarães et al. 2015). Therefore, the link between adjuvants and development of autoimmune disease must be extensively studied. Furthermore, new techniques must be developed to predict post-vaccination autoimmunity (Soriano et al. 2015). Additionally, safer and effective adjuvants and antigens must be developed for vaccine formulations.

2.4.2 Molecular Mimicry

Molecular mimicry is referred to mechanism by which infections agents present their antigens similar to host self-antigens (Arango et al. 2013). It suggests the homology

between the pathogen and self-antigens (Arango et al. 2013). Identical to the infectious agents, the antigens present in the vaccine formulations through molecular mimicry can elicit an autoimmune response (Segal and Shoenfeld 2018) (Table 2.1). Moreover, the adjuvants in the vaccine, through molecular mimicry, trigger an autoimmune response (Blank et al. 2013; Israeli et al. 2015; Guimarães et al. 2015). Therefore, the cross-reaction produced by molecular mimicry can activate the innate immune response, further activating self-reactive T and B cells, resulting in an autoimmune reaction (Arango et al. 2013) (Table 2.1, Fig. 2.2).

The European AS03-adjuvanted A (H1N1) pandemic vaccine has been significantly associated with autoimmune narcolepsy (Ahmed et al. 2014). Interestingly, a study reported homology between influenza nucleoprotein A and the extracellular domain of hypocretin neuropeptide (HCRT) receptor, suggesting that the influenza nucleoprotein A through molecular mimicry could trigger autoimmune narcolepsy (Ahmed et al. 2015). Additionally, the influenza A vaccine has been associated with the development of autoimmune GBS, since the vaccinated individuals developed anti-GM1 antibodies (Israeli et al. 2012; Segal and Shoenfeld 2018). Additionally, the HBV vaccine has been linked with several neurological symptoms. It has been suggested that the hepatitis surface antigens present in the HBV vaccine have similarities with myelin basic protein and myelin oligodendrocyte glycoprotein (Smyk et al. 2015). Thus, the surface antigen could lead to cross-reactivity resulting in autoimmune MS (Smyk et al. 2015). Additionally, the HBV vaccine has also been linked with increased ANA and neuro-lupus (Santoro et al. 2007). Moreover, HPV vaccines, potentially through molecular mimicry, have been shown to develop autoimmune conditions like SLE (Smyk et al. 2015).

2.4.3 mRNA-Based Vaccines: a Trigger to Autoimmunity

The mRNA-based vaccines consist of RNA encoding the antigen encapsulated by lipid nanoparticles (Wardell and Levings 2021). The lipid nanoparticles allow RNA to enter the host cells. By the process of electroporation, the mRNA enters the host cells. The mRNA then instructs the host cells to produce viral antigens, which leads to generation antibody response against the virus (Wardell and Levings 2021). The advantage of mRNA-based vaccine is its fast development and low cost manufacturing (Velikova and Georgiev 2021). The mRNA-based vaccines have gained attention after recent production of the recent SARS-CoV-2 vaccines by Pfizer-BioNTech and Moderna (Velikova and Georgiev 2021). The mRNA-based vaccines instruct the host cells to synthesize the S protein of SARS-CoV-2 virus (Velikova and Georgiev 2021).

The mRNA-based may increase the risk of developing autoimmune diseases. Similar to adjuvants mRNA vaccines may trigger innate immune response (Velikova and Georgiev 2021). The RNA in the vaccines can be recognized by RNA sensor in DCs leading to activation of innate immune response (Velikova and Georgiev 2021). Moreover, the single stranded mRNA can be recognized by pathogen-associated molecular patterns like Toll-like receptors (TLRs) such as TLR3, TLR7, and TLR8,

which can stimulate the innate immune response to produce pro-inflammatory cytokines like IFN-γ (Wang et al. 2021; Talotta 2021). Additionally, mRNA vaccines can increase cytokines and chemokines production after intradermal injections (Velikova and Georgiev 2021). Furthermore, by stimulating DCs maturation, inducing T and B cell response and through bystander activation of autoreactive lymphocytes, mRNA-based vaccines can trigger an autoimmune response (Wang et al. 2021; Talotta 2021; Velikova and Georgiev 2021).

2.4.4 Other Mechanisms

Immune mechanisms such as bystander activation, epitope spreading, cytokines production, and polyclonal activation of B cells can lead to vaccine induced autoimmunity (Agmon-Levin et al. 2009a). Through bystander activation the inflammatory response produced against the antigens present in the vaccines can result in activation of T and B cells with different specificity (Arango et al. 2013). The non-antigenic activation further contribute to autoimmune response through pathways such as inflammatory response, cytokines production, chemokines, PAMPs, etc. (Pacheco et al. 2019). Moreover, autoimmune response can be generated by vaccines through epitope spreading, where the spatial proximity and similarities between microbial epitopes and self-epitopes results in autoimmune response (Arango et al. 2013). Additionally, cross-reactivity can lead to autoantibody production and self-reactive $CD4^+$ and $CD8^+$ T cells activation (Arango et al. 2013). Furthermore, viral antigens in the vaccines may promote ASIA symptoms (Agmon-Levin et al. 2009a). Additionally, viral antigens present in the vaccines can lead to polyclonal activation of B and T cells, suppression of Tregs, cytokine storm, autoantibody production, altered self-antigens, induction of novel antigens, resulting in development of autoimmunity post-vaccination (Agmon-Levin et al. 2009a; Blank et al. 2013; Arango et al. 2013; Israeli et al. 2015; Smyk et al. 2015; Guimarães et al. 2015).

2.5 Vaccines Reported for Development of Autoimmunity

Autoimmune diseases are complex conditions that can arise from multiple factors, including genetics, epigenetics, environment, infections, stress (Wang et al. 2015). Recent studies have suggested the involvement of vaccines in the development of autoimmune diseases (Cohen and Shoenfeld 1996; Guimarães et al. 2015) (Table 2.2). Similar to infections, the vaccine, through molecular mimicry, can lead to autoimmune reactions (Segal and Shoenfeld 2018) (Fig. 2.2). Additionally, adjuvants, preservatives present in the vaccine can lead to autoimmune-related adverse reactions (Israeli et al. 2015) (Fig. 2.2). Here in this section, we discuss the vaccines which have been reported to develop autoimmunity.

Table 2.2 List of vaccines involved in the induction of autoimmunity

Vaccines	Autoimmune disease/manifestations	Reference
HBV vaccine	ASIA, Multiple Sclerosis, GBS, neuropathy, optic neuritis, myopathy, myasthenia gravis, chronic fatigue syndrome, Gulf-War syndrome, arthritis, vasculitis's, SLE, antiphospholipid syndrome, alopecia, thrombocytopenia, graves' disease, and glomerulonephritis	Matsui et al. (1996), Wise et al. (1997), Eliot (1998), Zaas et al. (2001), Geier and Geier (2004), Bogdanos et al. (2005), Ni et al. (2007), Altman et al. (2008), Orbach and Tanay (2009), Agmon-Levin et al. (2009b), Stübgen (2010), Salemi and D'Amelio (2010), Shoenfeld and Agmon-Levin (2011), Blank et al. (2013), Smyk et al. (2015)
MMR vaccine	Acute ITP, respiratory tract infection, erythema, pain, swelling, fever, aseptic meningitis, encephalitis, optic neuritis, Guillain-Barre syndrome, thrombocytopenia, hemolytic uremic syndrome, and hemolytic anemia	Nieminen et al. (1993), Abedi et al. (2012), Lievano et al. (2012), Israeli et al. (2015), Perricone et al. (2015), Guimarães et al. (2015), Segal and Shoenfeld (2018)
Influenza vaccine	ASIA, GBS, vasculitis, SLE, antiphospholipid syndrome, inflammatory myopathy, stills disease, juvenile idiopathic arthritis, narcolepsy, MS, acute disseminated encephalomyelitis (ADEM), and ITP	Rahier et al. (2011), Van Kerkhove et al. (2011), Han et al. (2011), Ferri et al. (2012), Blank et al. (2012, 2013), Poland and Jacobsen (2012), Bachi et al. (2013), Duggal et al. (2013), Jara et al. (2015), Guimarães et al. (2015), Segal and Shoenfeld (2018)
Human papilloma virus vaccine	ASIA, GBS, MS, ADEM, SLE, ITP, severe myalgia, polyarthralgia, anorexia, skin rash	Slade et al. (2011), Gatto et al. (2013), Tomljenovic and Shaw (2015), Genovese et al. (2018)
Meningococcal vaccine	GBS, Henoch–Schönlein purpura, Bullous pemphigoid, juvenile idiopathic arthritis	Passaro et al. (2015)
Pneumococcal vaccine	ITP, RA, SLE, and autoimmune hemolytic anemia	Borella et al. (2015)
BCG vaccine	Arthritis, T1DM, MS, dermatomyositis, Takayasu arteritis, Kawasaki disease	Bernini et al. (2015)
Yellow fever vaccines	RA, SLE, spondyloarthropathies, systemic sclerosis, arthralgia, myalgia	Levy and Rezende (2015)
SARS-CoV-2 vaccine	A rare case of autoimmune hepatitis, Alopecia areata	McShane et al. (2021), May Lee et al. (2022)

2.5.1 Hepatitis B Vaccines

Hepatitis B virus (HBV) is a DNA virus of the *Hepadnaviridae* family responsible for life-threatening liver viral infection (Liang 2009). HBV is transmitted from mother to child at birth; moreover, it can be spread by exposure to infected blood,

body fluids, needle stick injury, tattooing, piercing etc. (Liang 2009). The symptoms of HBV include acute illness, jaundice, fatigue, nausea, and vomiting (Liang 2009). Severe cases include chronic infections, which could lead to cirrhosis, liver cancer, and death (Liang 2009). The HBV vaccine protects against HBV infection and the vaccine is recommended after birth within 24 h, followed by the second dose 4 weeks later (Das et al. 2019).

Studies have highlighted the involvement of the HBV vaccine with autoimmunity by cross-reactivity of the HBsAg antigens and adjuvants included in the vaccine (Smyk et al. 2015). Moreover, HBV vaccines have been linked with ASIA (Shoenfeld and Agmon-Levin 2011; Smyk et al. 2015). Additionally, studies have reported molecular mimicry between hepatitis B surface antigens HBsAg and myelin antigens (Bogdanos et al. 2005). The vaccinated individuals develop antibodies against HBsAg, which cross-react with myelin basic protein and myelin oligodendrocyte glycoprotein, leading to autoimmune multiple sclerosis post HBV vaccinations (Matsui et al. 1996; Eliot 1998; Smyk et al. 2015). Additionally, HBV vaccinations have been linked with neuromuscular disorders like GBS, neuropathy, optic neuritis, myopathy, myasthenia gravis, chronic fatigue syndrome, Gulf-War syndrome (Orbach and Tanay 2009; Stübgen 2010; Salemi and D'Amelio 2010; Smyk et al. 2015). Additionally, autoimmune rheumatic disorders such as arthritis, vasculitis, SLE, antiphospholipid syndrome have been linked with HBV vaccinations (Zaas et al. 2001; Agmon-Levin et al. 2009b; Blank et al. 2013; Smyk et al. 2015) (Table 2.2). Additionally, alopecia, dermatomyositis have also been reported after HBV vaccine immunization (Wise et al. 1997; Altman et al. 2008). Moreover, thrombocytopenia, Graves' disease, and glomerulonephritis have also been associated with the HBV vaccine (Geier and Geier 2004; Ni et al. 2007; Smyk et al. 2015).

The aluminum-related adjuvants present in the HBV vaccine have been linked with autoimmunity (Israeli et al. 2015; Smyk et al. 2015). The aluminum salts activate the DCs and pro-inflammatory cytokines (IL-2 and IL-17) production (Israeli et al. 2015). Additionally, aluminum based adjuvants have been associated with quantitative and qualitative defects in Tregs (Agmon-Levin et al. 2009a; Israeli et al. 2015). In particular, the HBV vaccine responders showed reduced levels of Tregs (Agmon-Levin et al. 2009a; Israeli et al. 2015). Thus, the impaired Tregs and increased inflammation after HBV vaccination can lead to severe autoimmune reactions.

2.5.2 Measles, Mumps, and Rubella (MMR) Vaccines

The MMR vaccine protects against these three severe viral illnesses (measles, mumps, and rubella virus infection). MMR vaccine is recommended for vaccinations in children less than 1 year of age (Wellington and Goa 2003). The measles virus causes fever, cough, runny nose, conjunctivitis, and rash on the entire body (Misin et al. 2020). Serious complications of measles can include pneumonia (Misin et al. 2020), whereas in older children it can cause Sub-acute sclerosing

panencephalitis (SSPE) (Jafri et al. 2018). Mumps can cause swelling and pain in the parotid glands, in the testicles can cause infertility (Rubin et al. 2015). Rubella is also known as German measles, and it causes a mild rash (Shafayi and Mohammadi 2021). It can cause severe implications in pregnant women, such as congenital disabilities, deafness, and heart defects (Shafayi and Mohammadi 2021).

MMR vaccines are generally considered safe; however, its adverse effects were reported in 30.5 cases per million doses (Lievano et al. 2012). The adverse effects were respiratory tract infection, erythema, pain, swelling, fever (Perricone et al. 2015). Moreover, 136 temporally associated deaths have been reported, suggesting the MMR vaccination could trigger autoimmune reactions (Perricone et al. 2015). Evidence has suggested the involvement of acute ITP post MMR vaccination (Nieminen et al. 1993). Usually, the occurrence of ITP after MMR vaccination was not severe, self-limited, and non-life-threatening (Perricone et al. 2015). Apart from this, MMR vaccines have also been associated with arthralgia and arthritis (Abedi et al. 2012; Perricone et al. 2015). Studies suggest that the rubella component of the vaccine is primarily responsible for arthritis (Abedi et al. 2012; Perricone et al. 2015). Apart from this, the MMR vaccination can cause autoimmune manifestations like aseptic meningitis, encephalitis, optic neuritis, Guillain-Barre syndrome, thrombocytopenia, hemolytic uremic syndrome, and hemolytic anemia (Perricone et al. 2015) (Table 2.2). Thus, MMR vaccination accounts for several autoimmune reactions; however, the exact underlying mechanism is still unclear (Perricone et al. 2015). It has been suggested that the MMR vaccine could cause these manifestations by molecular mimicry, adjuvants, preservatives in the formulations (Israeli et al. 2015; Guimarães et al. 2015; Segal and Shoenfeld 2018). Although the autoimmune manifestation after MMR vaccination is rare and mostly self-limiting, the development of such autoimmune reactions cannot be ignored. Future studies must investigate the long-term safety aspects of the MMR vaccines.

2.5.3 Influenza Vaccine

Influenza virus belongs to the Orthomyxoviridae family, and it causes respiratory tract infection (Javanian et al. 2021). There are four types of influenza viruses: A, B, C, D, and influenza A viruses cause global flu epidemics (Javanian et al. 2021). They are divided into subtypes based on two surface proteins, hemagglutinin (HA) and neuraminidase (NA) (Javanian et al. 2021). There are 18 different HA and 11 different NA (Javanian et al. 2021). There are more than 130 different types of influenza viruses detected (Javanian et al. 2021). The currently circulating influenza virus is H1N1 which is related to the 2009 flu pandemic (Nypaver et al. 2021). As influenza viruses acquire frequent mutations in the HA and NA genes, seasonal influenza vaccines are recommended yearly (Nypaver et al. 2021).

Studies have highlighted that influenza vaccines can stimulate autoantibodies production; moreover, pregnant women experience severe complications (Van Kerkhove et al. 2011; Bachi et al. 2013). Influenza vaccines have also been associated with autoimmune diseases like GBS (Greene et al. 2012). Furthermore,

there is an increased risk of ASIA post influenza vaccination (Jara et al. 2015). Additionally, influenza vaccines have been associated with vasculitis, SLE, RA, antiphospholipid syndrome, inflammatory myopathy, stills disease, juvenile idiopathic arthritis, narcolepsy, MS, acute disseminated encephalomyelitis (ADEM), and ITP (Rahier et al. 2011; Han et al. 2011; Ferri et al. 2012; Blank et al. 2012; Poland and Jacobsen 2012; Duggal et al. 2013; Jara et al. 2015) (Table 2.2). Mechanism underlying autoimmune reactions are unknown; however, bystander activation, molecular mimicry, and adjuvants present in vaccines can trigger autoimmune response post influenza vaccinations (Blank et al. 2013; Jara et al. 2015; Guimarães et al. 2015; Segal and Shoenfeld 2018) (Table 2.1).

2.5.4 Human Papilloma Virus (HPV) Vaccine

The HPV virus is a DNA virus belonging to the papillomaviridae family (Brentjens et al. 2002). The HPV virus causes genital warts and cervical, anus, and throat cancers (Brentjens et al. 2002). There are more than 100 varieties of HPV, and it is transmitted through skin-to-skin contact (Brentjens et al. 2002). Moreover, HPV is considered to be one of the most common sexually transmitted diseases (Brentjens et al. 2002). In rare cases, HPV can be transmitted from pregnant women to newborn babies during birth, leading to recurrent respiratory papillomatosis in the infants (Brentjens et al. 2002). In the last decade, vaccines have been developed for several HPV types that prevent HPV and associated morbidities (Cheng et al. 2020).

Evidence has suggested the involvement of the HPV vaccine in the development of GBS, MS, ADEM (Slade et al. 2011; Tomljenovic and Shaw 2015). Moreover, the HPV vaccine has been linked with ASIA-related symptoms (Tomljenovic and Shaw 2015). Furthermore, vaccines have been related to autoimmune reactions such as SLE, ITP (Gatto et al. 2013; Tomljenovic and Shaw 2015). Additionally, post-vaccination individuals suffer from severe myalgia, polyarthralgia, anorexia, and skin rash (Tomljenovic and Shaw 2015). Moreover, antinuclear antibodies, anti-Ro (SSA), anti-La (SSB) antibodies, and anti-dsDNA antibodies have been observed post-HPV vaccination (Gatto et al. 2013; Tomljenovic and Shaw 2015) (Table 2.2). Despite such evidence, recently it has been reported that there is no association between HPV vaccines with autoimmune diseases (Genovese et al. 2018). However, the HPV vaccine, through molecular mimicry and adjuvants, preservatives can cause autoimmune reactions (Guimarães et al. 2015; Segal and Shoenfeld 2018) (Table 2.1). Therefore, future investigations must focus on identifying risk factors and autoimmune reactions post HPV vaccinations.

2.5.5 SARS-CoV-2 Vaccines

The COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused critical respiratory illness (Singhal 2020; Shoenfeld 2020; Liu et al. 2021). More than 3.7 million deaths have been reported due to the COVID-19.

Previous studies suggest that COVID-19 patients develop various autoimmune conditions like Miller Fisher syndrome, Antiphospholipid antibodies, thrombosis, Guillain-Barre syndrome, SLE, Kawasaki disease, autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura (ITP) (Galeotti and Bayry 2020; Ehrenfeld et al. 2020; Cavalli et al. 2020; McMillan et al. 2021; Liu et al. 2021). Moreover, studies have also found that patients develop a range of autoantibodies and cytokine storm post COVID-19 (McMillan et al. 2021; Ryabkova et al. 2021; Chang et al. 2021), suggesting SARS-CoV-2 as a trigger for autoimmunity (Halpert et al. 2021; Dotan and Shoenfeld 2021; Dotan et al. 2021a). Additionally, the autoimmune complications arising from SARS-CoV-2 infection suggest COVID-19 as a classical example for ASIA syndrome (Halpert and Shoenfeld 2020).

The swift vaccine development and approval of COVID-19 vaccines have led to a significant reduction in the COVID-19 cases (Kyriakidis et al. 2021). However, reports suggest that the COVID-19 vaccine might contribute to various inflammatory and autoimmune diseases (Galeotti and Bayry 2020; McMillan et al. 2021; Liu et al. 2021). Molecular mimicry is one of the mechanisms by which COVID-19 vaccines trigger an autoimmune response (Liu et al. 2021). Additionally, SARS-CoV-2 spike glycoprotein has resemblances with mammalian proteomes (Kanduc and Shoenfeld 2020). Furthermore, molecular mimicry between SARS-CoV-2 and the female reproductive system has been reported (Dotan et al. 2021b). Thus, molecular mimicry could be a potential mechanism contributing to SARS-CoV-2 associated autoimmune complications (Kanduc and Shoenfeld 2020). Apart from molecular mimicry, mRNA vaccines may give rise to an autoimmune response (Talotta 2021). Before translation, mRNA binds to pattern recognition receptors, toll-like receptors (TLR3, TLR7, and TLR8) and stimulate the innate immune response leading to production of pro-inflammatory cytokines like IFN-γ (Talotta 2021) (Table 2.1).

Though, there is a lack of association for the development of autoimmune disease post-COVID-19 vaccinations, a rare case of autoimmune hepatitis after the COVID-19 mRNA vaccine has been reported (McShane et al. 2021) (Table 2.2). Moreover, COVID-19 vaccines have been associated with development of alopecia areata (May Lee et al. 2022). Additionally, mRNA vaccines have shown to elicit autoantibodies post COVID-19 vaccinations (Wang et al. 2021). Moreover, immune-mediated disease flares or new-onset disease have been observed in 27 subjects following RNA/DNA SARS-CoV-2 vaccinations (Watad et al. 2021). Furthermore, the autoimmune complications after SARS-CoV-2 infections suggest a possibility for the development of autoimmunity (Galeotti and Bayry 2020; McMillan et al. 2021; Liu et al. 2021). Therefore, future studies must explore the possible relationship between COVID-19 vaccinations and the development of autoimmunity, which could lead to early identification of mechanisms related to vaccine induced, and natural infection-induced, complications that could adversely impact vaccine effectiveness and safety (Kostoff et al. 2020).

2.5.6 Other Vaccines

The other vaccines such as Meningococcal vaccines have been associated with GBS, Henoch-Schönlein purpura, Bullous pemphigoid, juvenile idiopathic arthritis (Passaro et al. 2015) (Table 2.2). Furthermore, pneumococcal vaccines have been associated with ITP, RA, SLE, and Autoimmune hemolytic anemia (Borella et al. 2015) (Table 2.2). Additionally, BCG vaccination is associated with arthritis, T1DM, MS, dermatomyositis, Takayasu arteritis, Kawasaki disease (Bernini et al. 2015) (Table 2.2). Moreover, the Yellow fever vaccines have been associated with RA, SLE, spondyloarthropathies, systemic sclerosis, arthralgia, myalgia (Levy and Rezende 2015) (Table 2.2).

2.6 Conclusions

Overall, the studies suggest vaccines can develop autoimmune and inflammatory reactions through molecular mimicry and cross-reactivity. Moreover, the advancement of vaccine research and the development of a novel approach for vaccination may raise a concern over the safety aspect of vaccines. Additionally, the adjuvants and preservatives used in the vaccines may cause complications leading to autoimmune triggers. However, the autoimmune and inflammatory reactions developed after vaccinations are very rare. Given the benefits of modern vaccines, currently, the risk to benefits ratio leans towards vaccines. However, future studies must focus on the relationship between vaccines and autoimmune reactions. Moreover, studies must investigate the genetic susceptibility of individuals before vaccine administrations. Additionally, research must be carried out to develop safe and effective adjuvants for vaccine formulations.

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COVID-19 and Autoimmunity

3

Prashant S. Giri, Shahnawaz D. Jadeja, Yehuda Shoenfeld, and Mitesh Kumar Dwivedi

Abstract

Coronavirus disease 2019 (COVID-19), caused by the continuously evolving novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been a global health concern since the start of pandemic. Apart from other COVID-19 associated complications, emerging studies have suggested autoimmune manifestations following SARS-CoV-2. Additionally, autoantibodies have been detected in COVID-19 patients. COVID-19 can lead to autoimmune manifestations, through various mechanisms such as molecular mimicry, bystander activation, cytokine storm, generation of autoantibodies, and genetic susceptibility. Several autoimmune diseases like Guillain-Barre syndrome, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune thyroid diseases, Kawasaki disease, and Alopecia areata have been linked with COVID-19. Additionally, autoimmune diseases have been linked with the increased risk of severe illness and mortality after SARS-CoV-2 infection. Therefore, understanding the pathophysiology of COVID-19 associated autoimmunity can aid in management and treatment of COVID-19.

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3.1 Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still prevalent even after 2 years of pandemic. It has affected almost all countries with around 450 million confirmed cases and over 6 million deaths as of March 14, 2022 (Singhal 2020; Shoenfeld 2020; Liu et al. 2021; Yazdanpanah and Rezaei 2022). Despite swift advancements in COVID-19 vaccine development, the SARS-CoV-2 virus is still a major health concern. Additionally, delayed or inadequate treatment causes major proportion of COVID-19 associated mortality (Yazdanpanah and Rezaei 2022). Clinical features, host genetic factors, co-morbidities, and autoimmune complications have been suggested to increase the risk of severe illness and mortality post-SARS-CoV-2 infection (Haberman et al. 2020; Freites Nuñez et al. 2020; Tan et al. 2021). Therefore, better risk stratification, clinical management, and better understanding of autoimmune complications after COVID-19 infection are required for COVID-19 management.

Autoimmune diseases are characterized by loss of immune tolerance leading to aberrant immune response against the hosts own tissues (Wang et al. 2015). The prevalence of autoimmune diseases is about 3–5% worldwide (Leslie and Hawa 1994; Wang et al. 2015). As viruses can induce type II and IV hypersensitivity, there is a possibility for COVID-19-mediated autoimmunity (Lin and Askonas 1981). Moreover, since the beginning of COVID-19 pandemic, various reports have been suggested for the appearance of COVID-19 manifestations after SARS-CoV-2 infection (Yazdanpanah and Rezaei 2022). Moreover, COVID-19 causes an hyperinflammatory state which results in autoimmune complications (Yazdanpanah and Rezaei 2022). Additionally, studies suggest that SARS-CoV-2 infection can lead to various autoimmune disease like Miller Fisher syndrome, Antiphospholipid antibodies (APS), thrombosis, Guillain-Barre syndrome (GBS), systemic lupus erythematosus (SLE), Kawasaki disease, autoimmune hemolytic anemia, and idiopathic thrombocytopenic purpura (ITP) (Galeotti and Bayry 2020; Ehrenfeld et al. 2020; Cavalli et al. 2020; McMillan et al. 2021; Liu et al. 2021). In addition, the autoimmune complications arising from SARS-CoV-2 infection suggest COVID-19 as a classical example for autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) also known as “Shoenfeld’s syndrome” (Halpert and Shoenfeld 2020).

The SARS-CoV-2 infection can lead to autoimmunity through various mechanisms such molecular mimicry, bystander activation, cytokine storm, production of autoantibodies, and genetic susceptibility (Moran and Prendergast 2001; Ercolini and Miller 2009; Smatti et al. 2019; Ragab et al. 2020; Icenogle 2020;

Liu et al. 2021; Bergamaschi et al. 2021a, b). Moreover, autoimmune complications after SARS-CoV-2 infection can lead to increased disease severity (Haberman et al. 2020; Freites Nuñez et al. 2020; Tan et al. 2021). However, in the current scenario a far better understanding regarding the autoimmune complications after SARS-CoV-2 infection is needed; therefore this chapter discusses the different autoimmune conditions that develop after SARS-CoV-2 infection and the possible mechanisms involved to establish a possible association of COVID-19 and autoimmunity.

3.2 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Coronaviruses are diverse group of viruses, belonging to the Coronaviridae family (González et al. 2003). It infects different animals and causes mild to severe respiratory illness in humans (Hu et al. 2020). The name coronavirus was derived from the Greek word crown refereeing to crown or corona like appearance (House et al. 2021). They are enveloped RNA viruses with club like spikes on their surfaces (Fig. 3.1). Its laboratory diagnosis is generally done by detecting viral RNA by real time PCR. The viruses mutate rapidly, and account for almost 15% of common cold (House et al. 2021). In 2002 and 2012, two highly pathogenic coronaviruses strains: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged causing deadly respiratory illnesses (Hu et al. 2020). At the end of 2019, SARS-CoV-2 pandemic emerged from Wuhan city of China. The virus spreads rapidly and surpassed SARS and MERS infections quickly. The outbreak become a global threat to public health (House et al. 2021). The SARS-CoV-2 virus was successfully isolated from Wuhan sea food market in the first week of January (Kumar and Malviya 2020). The SARS-CoV-2 viral structure consists of helical nucleocapsid with 30 kb plus stranded RNA genome. The viral RNA interacts with nucleocapsid (N) protein, and the virus structure consists of structural spike protein (S), membrane protein (M) and envelope protein (E) (Fig. 3.1) (Wang et al. 2020).

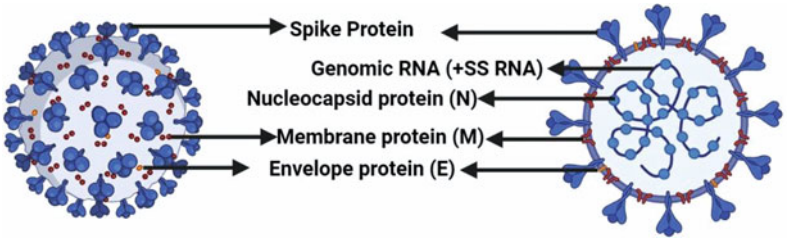

Fig. 3.1 Structure of SARS-CoV-2 virus. SARS-Cov-2 is an enveloped, positive stranded RNA virus with four major structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins

The general mechanism by which the virus enters host cells is similar to other coronaviruses. The virus enters the host cells by attachment of S-protein to the angiotensin-converting enzyme 2 receptor (ACE2), thus the SARS-CoV-2 virus has a tropism to pulmonary, hepatic, gastrointestinal, and renal human cells (Santos et al. 2020). The interaction of viral S protein to ACE2 receptors triggers viral endocytosis and endosome formation. The S protein consists of S1 and S2 subunits, and the proteolytic cleavage of S1 protein by cellular proteases exposes S2 fusion peptide allowing the fusion of viral envelope to endosome membrane and release of capsid to the cell cytoplasm (Santos et al. 2020; Walls et al. 2020). The positively stranded viral RNA consisting of ORF1a and ORF1b are translated to produce non-structural proteins (NSPs) (Santos et al. 2020). The NSPs then form replication complex responsible for replication, RNA synthesis and sub-genomic RNA formation (Santos et al. 2020; Chen et al. 2020). The sub-genomic RNA is translated to produce S, E, and M structural proteins (Li et al. 2020). The replicated viral genome is encapsulated by the N protein and assembled with the structural proteins to form the complete virion. The complete virion is transported through cellular vesicles to the cell surface and released out by exocytosis (Santos et al. 2020; Li et al. 2020).

3.3 Virus Infection and Autoimmunity

Autoimmune diseases are characterized as an aberrant immune responses, resulting due to recognition of self-antigens as non-self-antigens (Giri et al. 2022). There are more than 80 autoimmune diseases, and their prevalence ranges from 3% to 5% worldwide (Ercolini and Miller 2009; Wang et al. 2015). Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), etc. have been a global health concern and contribute significantly to the mortality and morbidity associated with autoimmune diseases (Wang et al. 2015). There is no cure for most autoimmune diseases, and the current treatment options generally only provide symptomatic reliefs (Chandrashekara 2012). Moreover, despite recent advancements in the field, the exact etiology for autoimmune diseases is unclear. Several factors like genetics, epigenetics, stress, environmental factors have been suggested to trigger the autoimmune response (Costenbader et al. 2012). Apart from these, studies also suggest that multiple factors including infections, nutrition, stress, microbiota, tobacco, smoke, pharmaceutical agents, hormones, ultraviolet light, heavy metals, vaccines can trigger the development of autoimmune diseases (Shoenfeld et al. 2000; Costenbader et al. 2012).

Viruses are considered to be one of the major environmental trigger responsible for the development of autoimmunity. Multiple mechanisms such as molecular mimicry, bystander activation, cross-reaction, epitope spreading, cytokine storm have been suggested to play a crucial role in viral infection induced autoimmunity (Ercolini and Miller 2009; Smatti et al. 2019; Liu et al. 2021). Moreover, viruses can induce Type II and IV hypersensitivity (Lin and Askonas 1981) and can cause ASIA syndrome (Halpert and Shoenfeld 2020). Additionally, the viral infections induced

autoimmunity has been observed in experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS), West Nile virus (WNV)-mediated myasthenia gravis (MG), Theiler's murine encephalomyelitis virus-CNS autoimmunity, Epstein–Barr virus (EBV), and measles virus induced MS and SARS-CoV-2 virus induced autoimmunity (Miller et al. 1997; Tucker and Andrew Paskauskas 2008; Constantinescu et al. 2011; Lünemann 2012; Getts et al. 2013; Leis et al. 2014; Smatti et al. 2019; Galeotti and Bayry 2020; Ehrenfeld et al. 2020; Cavalli et al. 2020; McMillan et al. 2021; Liu et al. 2021).

3.3.1 SARS-CoV-2 Induced Autoimmunity

Emerging studies have suggested COVID-19 patients develop various autoimmune manifestations like GBS, ITP, RA, SLE, T1DM, Miller Fisher syndrome, Kawasaki disease, Autoimmune thyroid diseases, Antiphospholipid antibodies, Vitiligo, Alopecia areata, Cold agglutinin syndrome thrombosis, APS and autoimmune hemolytic anemia (Galeotti and Bayry 2020; Ehrenfeld et al. 2020; Cavalli et al. 2020; Tung et al. 2021; McMillan et al. 2021; Ruggeri et al. 2021; Liu et al. 2021; Post et al. 2021; Edwards et al. 2021; Bhagat et al. 2021; Dewanjee et al. 2021; Tammaro et al. 2022). Moreover, studies have also found that patients develop a range of autoantibodies and cytokine storm post-COVID-19 (McMillan et al. 2021; Ryabkova et al. 2021; Chang et al. 2021), suggesting that SARS-CoV-2 infection can trigger autoimmunity (Halpert et al. 2021; Dotan and Shoenfeld 2021; Dotan et al. 2021a). Additionally, the autoimmune complications arising from SARS-CoV-2 infection suggest COVID-19 as a classical example for ASIA syndrome (Halpert and Shoenfeld 2020). Multiple mechanisms like molecular mimicry, cytokine storm, production of autoantibodies, and genetic susceptibility can result in SARS-CoV-2 induced autoimmunity (Moran and Prendergast 2001; Ercolini and Miller 2009; Smatti et al. 2019; Ragab et al. 2020; Icenogle 2020; Liu et al. 2021; Bergamaschi et al. 2021a, b). These mechanisms are discussed in the following sections.

3.3.1.1 Molecular Mimicry

Molecular mimicry occurs when infectious agents such as viruses present antigens similar to host self-antigens (Arango et al. 2013). Thus, the cross-reaction between SARS-CoV-2 viral antigens and self-antigens can activate self-reactive T and B mediated autoimmune response (Arango et al. 2013). Experimental evidence suggests that viruses such as Herpes simplex virus (HSV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) can trigger various autoimmune diseases through molecular mimicry (Moran and Prendergast 2001; Smatti et al. 2019). Additionally, recent studies have also suggested the role of EBV and CMV in the development of vitiligo—skin autoimmune disease (Doğan et al. 2014; Dwivedi et al. 2018).

Previously, human coronaviruses CoV-229E and HCoV-OC43 have been linked with MS (Salmi et al. 1982; Stewart et al. 1992; Talbot et al. 1996; Arbour et al. 2000; Moody et al. 2021). Furthermore, cross reactive T cells immune response has

been detected between myelin and HCoV-OC43 antigens (Arbour et al. 2000; Moody et al. 2021). Similarly, SARS-CoV-1 has been found to be associated with autoimmune diseases by cross reactivity (Wang et al. 2004; Moody et al. 2021). Patients with autoimmune diseases such as RA, SLE, Sjogren's syndrome were found positive for SARS-CoV-1 antibodies, despite lacking any previous SARS-CoV-1 infections (Wang et al. 2004; Moody et al. 2021). Therefore, these studies indicate that like other coronaviruses, SARS-CoV-2 can also lead to autoimmune diseases.

In addition, the spike glycoprotein of SARS-CoV-2 virus has structural resemblances with mammalian proteomes (Kanduc and Shoenfeld 2020). The study suggested SARS-CoV-2 proteome and the human proteins PARP14, PARP9, and MACROD1, may potentially behave as molecular mimics, which may result in activation of autoreactive $CD8^+$ and $CD4^+$ T cells mediated autoimmune response (Kanduc and Shoenfeld 2020). Moreover, the study found that NSP3 protein consist of an LKH tripeptide which is homologous with human proteome and these homologous regions may prompt autoreactive B cells to produce antibodies for these epitopes (Kanduc and Shoenfeld 2020). Furthermore, molecular mimicry between SARS-CoV-2 and the female reproductive system has been reported (Dotan et al. 2021b). It has also been reported that molecular mimicry between SARS-CoV-2 antigens and neural antigens can lead to GBS (Shoraka et al. 2021) (Table 3.1). Similarly, molecular mimicry of SARS-CoV-2 antigens with Ankyrin-1 (Ank-1) protein has been suggested to cause Autoimmune hemolytic anemia (Angileri et al. 2020). Apart from these, molecular mimicry may be involved in autoimmune manifestations like ITP, SLE, and APS, post-COVID-19 (Table 3.1) (Bhattacharjee and Banerjee 2020; Tung et al. 2021; Gracia-Ramos et al. 2021). It has been suggested that such molecular mimics through resident antigen presenting cells can promote autoreactive T and B cells response (Fig. 3.2) (Kanduc and Shoenfeld 2020). Thus, molecular mimicry could be a potential mechanism contributing to SARS-CoV-2 associated autoimmune complications (Kanduc and Shoenfeld 2020).

3.3.1.2 Bystander Activation

Bystander activation is an another crucial mechanism by which SARS-CoV-2 infection can cause autoimmunity (Arango et al. 2013). Here the inflammatory response against SARS-CoV-2 can contribute to activation of self-reactive T and B cells (Fig. 3.1) (Arango et al. 2013); thus these non-antigenic activation can lead to an autoimmune response (Pacheco et al. 2019). The autoimmune response mediated by SARS-CoV-2 can be triggered by pathogen-associated molecular patterns (PAMPs), cytokines and chemokines. Viral infections such as Influenza virus, EBV, and CMV trigger bystander activation leading to autoimmune response mediated by self-reactive T cells, B cells, NK cells, and DCs (Fujinami et al. 2006; Arango et al. 2013; Jung et al. 2017; Dwivedi et al. 2018; Pacheco et al. 2019).

The evidence for SARS-CoV-2 infection mediated autoimmunity through bystander activation is suggested in patients with persistent COVID-19. The patients with persistent COVID-19 have highly activated innate immune cells (Phetsouphanh

Table 3.1 Various mechanisms of SARS-CoV-2 induced autoimmunity

Mechanism	Description/example	Reference
Molecular mimicry	Cross-reaction between SARS-CoV-2 viral antigens and self-antigens can activate self-reactive T and B mediated autoimmune response.	Arango et al. (2013), Angileri et al. (2020), Kanduc and Shoenfeld (2020), Bhattacharjee and Banerjee (2020), Tung et al. (2021), Dotan et al. (2021a, b), Gracia-Ramos et al. (2021)
	Spike glycoprotein of SARS-CoV-2 virus has structural resemblances with mammalian proteomes.	
	SARS-CoV-2 proteome and the human proteins PARP14, PARP9, and MACROD1, behave as molecular mimics, activating autoreactive $CD8^+$ and $CD4^+$ T cells.	
	LKH tripeptide of NSP3 protein is homologous with human proteome and may prompt autoreactive B cells to produce autoantibodies.	
	Molecular mimicry between SARS-CoV-2 and the female reproductive system has been reported.	
	SARS-CoV-2 antigens mimic Ank-1 protein leading to autoimmune hemolytic anemia.	
	SARS-CoV-2 molecular mimicry is involved in autoimmune manifestations like ITP, SLE, and APS syndrome.	
Bystander activation	Inflammatory response against SARS-CoV-2 can contribute to activation of self-reactive T and B cells.	Arango et al. (2013), Pacheco et al. (2019), Bergamaschi et al. (2021a, b), Phetsouphanh et al. (2022)
	Non-antigenic activation can lead to an autoimmune response.	
	Persistent COVID-19 patients have highly activated innate immune cells and immune and inflammatory abnormalities have been found to be persistent in severe disease for more than 60 days post-COVID-19.	
	Severe COVID-19 has delayed bystander $CD8^+$ T cell immune response.	
Cytokine storm	A life-threatening inflammatory syndrome (cytokine release syndrome) is involved elevated levels of cytokines and hyper immune cells activation.	Huang et al. (2020), Ragab et al. (2020), Icenogle (2020)
	Increased levels of IL-2, IL-17, IP10, MCP1, TNF-α, IL-1, and IFN-γ cytokines in severe COVID-19 patients.	

(continued)

Table 3.1 (continued)

Mechanism	Description/example	Reference
	Increased pro-inflammatory cytokines lead to activation of Th1 response, leading to infiltration of macrophages, neutrophils, and T cells from the circulation into the site of infection, which contribute to tissue and organ damage.	
Autoantibodies	Increased autoantibodies have been detected in severe COVID-19 patients.	Bastard et al. (2020), Zhou et al. (2020), Zuo et al. (2020), Vlachoyiannopoulos et al. (2020), Xiao et al. (2020), Franke et al. (2021)
	Increased ANA antibodies, anti-SSA/Ro antibodies, anti-SSA/Ro antibodies, anti-scl-70 antibodies and anti-U1-RNP antibodies were detected in severely ill COVID-19 patients.	
	70% of COVID-19 patients had autoantibodies against systemic autoimmune rheumatic disease.	
	Autoantibodies are detected against antiphospholipid antibodies, neuronal targets, IFN-γ, GM-CSF, IL-6, and IL-10.	
Innate immune mechanisms	SARS-CoV-2 RNA is recognized by DCs which activate innate immune response, and also induce autoreactive T and B cells response.	Wang et al. (2021), Talotta (2021), Velikova and Georgiev (2021)
	SARS-CoV-2 mRNA recognized by TLR3, TLR7, and TLR8 can prime the innate immune response to produce pro-inflammatory cytokines like IFN-γ.	
Genetic susceptibility	Individuals vulnerable to SARS-CoV-2 infection may also be susceptible to autoimmune diseases.	Sun et al. (2019), Zhao et al. (2019), Yu et al. (2021)
	HLA-B*15:27 and HLA-DRB1*04:06 are risk alleles for COVID-19 susceptibility.	
	HLA-DRB1*04:06 is a risk factor for autoimmune diseases.	

Ank-1 ankyrin-1, *PARP* poly (ADP-ribose) polymerase family member, *MACROD1* mono-ADP ribosyl hydrolase 1, *NSP3* non-structural protein 3, *ITP* immune thrombocytopenic purpura, *SLE* systemic lupus erythematosus, *APS* antiphospholipid syndrome, *IP10* interferon γ-induced protein 10, *MCP1* monocyte chemoattractant protein-1, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *ANA* antinuclear antigen antibodies, *Anti-SSA* anti–Sjögren's-syndrome-related antigen A, *Anti-scl-70* anti-systemic sclerosis-70, *Anti-U1-RNP* anti-U1-ribonucleoprotein, *TLR* toll-like receptor, *DCs* dendritic cells

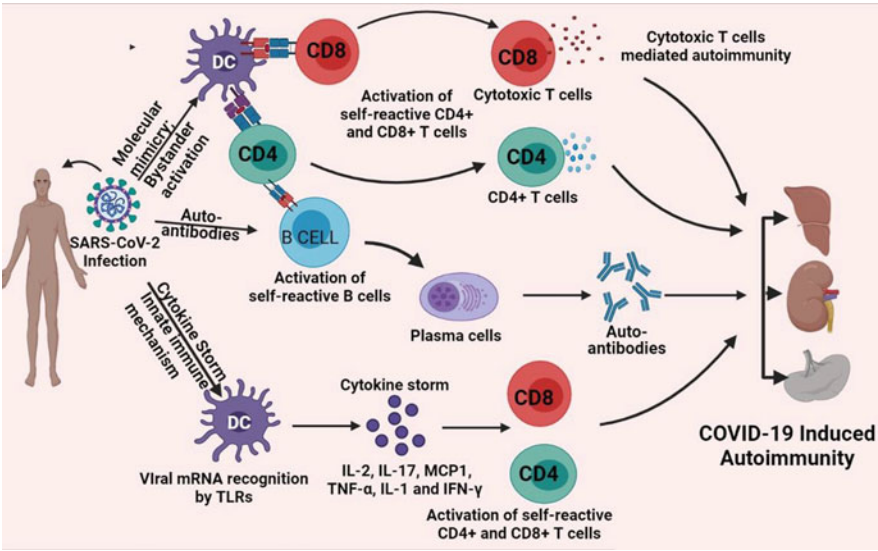

Fig. 3.2 Role of SARS-CoV-2 infection in development of autoimmunity. SARV-CoV-2 through molecular mimicry and bystander activation can promote autoreactive T and B cells response. Additionally, cytokine storm can lead to increased pro-inflammatory cytokines which further contribute to activation of Th1 response. Moreover, TLR sensing of viral RNA through resident antigen presenting cells can activate self-reactive adaptive response. Furthermore, the increased levels of autoantibodies detected in COVID-19 can result in tissue damage. Therefore, COVID-19 patients may develop various autoimmune diseases through various mechanisms such as molecular mimicry, bystander activation, cytokine storm, and production of autoantibodies

et al. 2022). Additionally, the patients had elevated expression of pro-inflammatory cytokines like type I IFN. Moreover, this elevated immune response was persistent for 8 months post-COVID-19 (Phetsouphanh et al. 2022). Additionally, patients with severe COVID-19 had delayed bystander $CD8^+$ T cell immune response (Table 3.1) (Bergamaschi et al. 2021a, b). Furthermore, this immune and inflammatory abnormalities have been found to be persistent in severe disease for more than 60 days post-COVID-19 (Table 3.1) (Bergamaschi et al. 2021a, b). In addition, evidence of heterologous T cell immunity between bacterial pathogens and SARS-CoV-2 further suggests that bystander activation is mediated by SARS-CoV-2 infection (Eggenhuizen et al. 2022). Overall, the above mentioned studies suggest that SARS-CoV-2 infection can trigger autoimmune response by bystander activation.

3.3.1.3 Cytokine Storm

Another mechanism by which SARS-CoV-2 infection can cause autoimmunity is cytokine storm (Ragab et al. 2020; Icenogle 2020). It is also called cytokine release syndrome, which is a life-threatening inflammatory syndrome involving elevated levels of cytokines and hyper immune cells activation (Ragab et al. 2020; Icenogle 2020). The severely ill COVID-19 patients have been characterized by elevated

cytokines, which is suggestive of immune dysregulation (Huang et al. 2020; Tay et al. 2020; Qin et al. 2020). The clinical features of severe COVID-19 suggested an increased levels of IL-2, IL-17, IP10, MCP1, TNF-α, IL-1, and IFN-γ cytokines (Table 3.1) (Huang et al. 2020). Furthermore, these increased pro-inflammatory cytokines led to activation of Th1 response and resulted in cytokine storm (Ragab et al. 2020; Icenogle 2020). The increase in cytokines also led to infiltration of macrophages, neutrophils, and T cells from the circulation into the site of infection (Ragab et al. 2020; Icenogle 2020), indicating that the elevated immune response can lead to tissue and organ damage. In addition, severe COVID-19 patients have been characterized by persistent inflammatory and persistent $CD8^+$ T cells response (Bergamaschi et al. 2021a, b). One recent study has suggested for higher levels of IL-6 in mortality cases (Ruan et al. 2020). Overall, the above mentioned studies suggest that increased cytokine levels post COVID-19 can lead to increased Th1 response and increased infiltration of immune cells to the site of infection, which might lead to COVID-19 mediated autoimmunity (Fig. 3.1) (Ragab et al. 2020; Icenogle 2020).

3.3.1.4 Autoantibodies

Increased levels of autoantibodies have been detected in COVID-19 patients with severe disease (Bastard et al. 2020; Zhou et al. 2020; Zuo et al. 2020; Vlachoyiannopoulos et al. 2020). Previous study suggested the presence of antinuclear antigen (ANA) antibodies, anti-SSA/Ro antibodies, anti-SSA/Ro antibodies, anti-scl-70 antibodies, and anti-U1-RNP antibodies in severely ill COVID-19 patients (Table 3.1) (Vlachoyiannopoulos et al. 2020). The study reported that 70% of COVID-19 patients had at least one of the systemic autoimmune rheumatic disease (Vlachoyiannopoulos et al. 2020); among which the most common antibodies are antiphospholipid antibodies (APLs) (Zuo et al. 2020; Xiao et al. 2020; Franke et al. 2021). These APLs are generally associated with APS (Xiao et al. 2020). Moreover, severe COVID-19 patients had the presence of antibodies against phospholipids (Zuo et al. 2020; Xiao et al. 2020; Franke et al. 2021). Severe COVID-19 patients with neurological symptoms also reported to exhibit autoantibodies against neuronal targets (Franke et al. 2021). Moreover, antibodies have been found against cytokines such as IFN-γ, GM-CSF, IL-6, and IL-10 (Table 3.1) (Bastard et al. 2020). One study has suggested that the LKH tripeptide of NSP3 protein homologous with human proteome may prompt autoreactive B cells to produce antibodies for these epitopes (Kanduc and Shoenfeld 2020). Thus, the presence of autoantibodies suggests that severe SARS-CoV-2 infection can result in autoimmune reaction (Fig. 3.1).

3.3.1.5 Innate Immune Mechanisms

The SARS-CoV-2 RNA can be recognized by DCs which can further activate innate immune response (Fig. 3.1) (Velikova and Georgiev 2021). Additionally, the single stranded mRNA recognized by PAMPs like Toll-like receptors (TLRs) such as TLR3, TLR7, and TLR8 can prime the innate immune response to produce pro-inflammatory cytokines like IFN-γ (Wang et al. 2021; Talotta 2021). Furthermore,

the DCs can then induce T and B cell response which can contribute to the autoimmune response (Table 3.1) (Wang et al. 2021; Talotta 2021; Velikova and Georgiev 2021).

3.3.1.6 Genetic Susceptibility

HLA-B*15:27 and HLA-DRB1*04:06 have been found to be risk alleles for COVID-19 susceptibility (Yu et al. 2021). Additionally, HLA-A*11 and HLA-B*40 have also been linked with COVID-19 infection (Table 3.1) (Warren and Birol 2020; Littera et al. 2020; Lorente et al. 2021; Yu et al. 2021). Interestingly, HLA-DRB1*04:06 has been found to be risk factor for autoimmune diseases (Table 3.1) (Sun et al. 2019; Zhao et al. 2019). These findings indicate a possible correlation between autoimmune diseases and COVID-19 severity and mortality (Yu et al. 2021). In addition, DRB1 and DQA1 have been associated with circulating IL-6 levels, which is a key inflammatory marker for COVID-19 severity (Ahluwalia et al. 2021). Overall, these findings indicate that individuals vulnerable to SARS-CoV-2 infection may also be susceptible to autoimmune diseases (Yu et al. 2021). However, studies analyzing such associations are scarce and future genetic association studies are warranted to establish the correlation between SARS-CoV-2 infection and autoimmune diseases.

3.4 Similarities Between COVID-19 Manifestations and Autoimmunity

Various clinical presentations extending from asymptomatic infection to lethal respiratory failure are observed in patients with COVID-19 disease caused by SARS-CoV-2. Moreover, it is also observed that many patients experience other long-term symptoms after the initial onset often extending beyond the original organ involved and this phenomena is known as post-acute sequelae of COVID-19 (PASC) (Knight et al. 2021). Apart from various post-COVID manifestations such as respiratory, cardiac, musculoskeletal, endocrine, etc., one of the key manifestations observed is the development of a detrimental immune reaction against self-tissue antigens (Mehandru and Merad 2022). Here, we discuss some of the major autoimmune diseases and syndromes reported to be associated with COVID-19, so far.

3.5 Autoimmune Complications of COVID-19

3.5.1 Guillain-Barre Syndrome

Guillain-Barré syndrome (GBS) is a severe immune mediated neuropathy with a global incidence of around 1–2 cases per million in a year. It is caused due to autoimmune damage to the peripheral nervous system characterized by rapidly developing motor weakness. It is believed to be triggered by a prior respiratory or gastrointestinal infection in most of the cases (Bragazzi et al. 2021). Hence, there

could be fair chances of GBS onset post-COVID-19 infection. The first case of GBS associated with SARS-CoV-2 infection was reported in China in a 61-years-old woman. Neurological examination revealed symmetric weakness and areflexia in both legs; however, in this case a pattern of para-infectious profile was observed instead of post-infection (Zhao et al. 2020). Various researchers around the world have reported the incidence of GBS in patients with COVID-19 (Yazdanpanah and Rezaei 2022). Till date, around 90% of GBS cases were reported in individuals above 50 years of age and almost two third of them were diagnosed after 2 weeks of SARS-CoV-2 infection. It is noteworthy that the clinical manifestations and severity in these GBS patients were like non-COVID GBS patients (Ramos-Casals et al. 2021).

3.5.2 Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is a hematological autoimmune disorder characterized by autoantibody mediated destruction of platelets resulting in increased bleeding risk (Cooper et al. 2021). The clinical course is often acute and severe in pediatric patients whereas around 64% of chronic cases are observed in adults. ITP has been reported to be associated with several viral infections such as EBV, CMV, HIV, and HCV (Liebman 2008; Elalfy and Nugent 2016). Reports have suggested the incidence of ITP in patients with SARS-CoV-2 infection, predominantly affecting patients of more than 50 years age displaying ITP manifestations such as purpura and mucosal bleeding (Ramos-Casals et al. 2021). In around 20% of cases, ITP occurred 3 weeks after COVID-19 onset; however, about 7% of ITP cases were also observed in asymptomatic COVID-19 patients. COVID-19 associated ITP could be due to the underlying immune dysregulation, genetic predisposition, and other mechanisms such as molecular mimicry, cryptic antigen expression, epitope spreading, etc. (Bhattacharjee and Banerjee 2020) (Table 3.2).

3.5.3 Kawasaki Disease

Kawasaki disease (KD), first reported by Japanese physician Tomisaku Kawasaki, is an acute febrile systemic vasculitides predominantly occurring in childhood (Beom Kim 2019). KD is manifested by inflammatory changes to the endothelial walls of arteries including coronary arteries, and coronary artery lesions may lead to serious complications as coronary artery ectasia/dilatation, coronary artery aneurysm, and acute myocardial infarction (Newburger et al. 2004). The onset of KD is generally between 6 months and 5 years of age with common symptoms such as fever, skin rash, diffuse mucosal inflammation, non-exudative conjunctivitis, cervical lymphadenopathy, etc. (Minich et al. 2007; Gatterre et al. 2012). Many SARS-CoV-2 infected children in UK were reported with systemic inflammatory syndrome features, similar to KD (Martinez et al. 2020). A few other cases of critically ill SARS-CoV-2 infected children presenting characteristics of systemic inflammation

Table 3.2 Autoimmune complications after COVID-19 infection

S. No.	Clinical manifestations	Possible mechanisms involved	Reference
1.	Guillain-Barre syndrome	Molecular mimicry between viral and neural antigens	Shoraka et al. (2021)
2.	Immune thrombocytopenic purpura	Underlying immune dysregulation, SOCS1 mutations, and other mechanisms including molecular mimicry	Bhattacharjee and Banerjee (2020)
3.	Kawasaki disease	Down regulation of ACE2 by SARS-CoV-2 through TNF-α	Amirfakhryan (2020)
4.	Autoimmune thyroid disease	Possibly due to the direct action of the SARS-CoV-2 virus on thyroid cells through ACE2 receptor	Ruggeri et al. (2021)
5.	Rheumatoid Arthritis	Hyperactivation of pro-inflammatory cytokine response by COVID-19 may be a potential causative factor	Dewanjee et al. (2021)
6.	Systemic Lupus Erythematosus	Molecular mimicry and cytokine storm could be involved	Gracia-Ramos et al. (2021)
7.	Type 1 Diabetes	β-cells by the pro-inflammatory cytokines induced by SARS-CoV-2	Edwards et al. (2021)
8.	Vitiligo	Due to a shift of the immune response towards adaptive type 1 in Vitiligo might be protective against SARS-CoV-2 infection	Post et al. (2021)
9.	Alopecia areata	Higher titers of IL-17 and type I interferons are believed to involved in the pathogenesis of COVID-19-associated Alopecia areata	Tammaro et al. (2022)
10.	Autoimmune hemolytic anemia	Molecular mimicry with Ankyrin-1 (Ank-1) protein	Angileri et al. (2020)
11.	Cold agglutinin syndrome (CAS)	SARS-CoV-2 virus may activate complement and upregulate anaphylatoxins (C3a and C5a) leading to hemolysis caused by cold agglutinins	Bhagat et al. (2021)
12.	Antiphospholipid syndrome	Molecular mimicry and endothelial dysfunction	Tung et al. (2021)
13.	Miller Fisher syndrome	Ganglioside mimicry by SARS-CoV-2 and generation of anti-GQ1b-IgG or anti-GD1b-IgG antibodies	Biswas et al. (2022)

and some features of KD were also reported. Verdoni et al., have reported that among ten, almost half of the COVID-19 infected children presented classical KD like manifestations and remaining were identified with incomplete KD (Verdoni et al. 2020).

3.5.4 Autoimmune Thyroid Diseases

Autoimmune thyroid diseases (AITDs), affecting about 2–5% of the population, are among the most prevalent autoimmune disorders, mainly comprising of Graves'

Disease (GD) and Hashimoto Thyroiditis (HT) (Dayan and Daniels 1996; Simmonds and Gough 2004). They are characterized by the loss of immune tolerance in addition to humoral and cell-mediated autoimmune response against thyroid gland (Dayan and Daniels 1996; Simmonds and Gough 2004). Interestingly, Vojdani et al., have demonstrated that SARS-CoV-2 antibodies cross reacted with different human tissues including thyroid (Vojdani et al. 2021). It has been observed that even patients with mild COVID-19 symptoms have shown complications of AITDs. In a cohort study, Lui et al., have reported thyroid dysfunctions in COVID-19 patients. They noticed that during the convalescence period, the incidence of thyroiditis was rare; however, they observed an imbalance in thyroid function test and detected anti-thyroid antibodies in these patients (Lui et al. 2021). In another report, Feghali et al., presented three cases of thyroid dysfunction which developed few weeks after the convalescence period of SARS-CoV-2 infection in patients without any previous history of thyroid disease. They observed a 38 years old woman developed hypo-thyroidism after 6 weeks of SARS-CoV-2 infection, a 33 years old female developed Grave's disease after 8 weeks of SARS-CoV-2 infection and another case of 41 years old female developed thyroiditis 6 weeks post SARS-CoV-2 infection (Feghali et al. 2021). It has been speculated that the thyroid related anomalies may occur due to a direct or indirect effects of SARS-CoV-2 infection on the gland. The plausible development of chronic thyroid autoimmunity and hypothyroidism has been also anticipated because of either a prior subacute thyroiditis or a viral trigger of autoimmunity in susceptible people (Ruggeri et al. 2021) (Table 3.2).

3.5.5 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by inflammatory changes of the synovial tissue of joints, cartilage and bone. RA is prevalent in around 0.06–1.27% population worldwide. Aberrations in the cellular and humoral immune response result in generation of autoantibodies in addition to lymphocyte infiltration into the synovium (Thanapati et al. 2017; Giri et al. 2021a; Almutairi et al. 2021). RA is a chronic multisystem autoinflammatory disorder manifested by joint pain, synovitis, stiffness, and muscle wasting around the involved joints (Mohammed 2020). Around 15% of the patients infected with SARS-Cov-2 were observed to have arthralgia at some point. Mukarram and colleagues have reported a case series of five patients who developed bilaterally symmetrical polyarthritis, without any previous history of any rheumatic disease. Moreover, the musculoskeletal manifestations were phenotypically like RA. Interestingly, these patients responded well to low-dose glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) (Mukarram et al. 2021). A few other studies have also reported presence of anti-citrullinated protein antibodies (ACPA) and flaring of RA in patients infected with SARS-CoV-2 (Vlachoyiannopoulos et al. 2020; Perrot et al. 2021). However, there is still a debate on the association of COVID-19 and RA that whether they are actually associated or mere a coincidence. Derksen et al., carried out a detailed investigation on 61 patients and observed that the seroprevalence of ACPA is not

significantly higher post SARS-CoV-2 infection and the patients demonstrating polyarthritis were resembling regular patients with RA and hence, they speculated that RA after COVID-19 may be coincidence rather than connected (Derksen et al. 2021).

3.5.6 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with inconsistent manifestations predominantly affecting women (Barber et al. 2021). It is characterized by an overall loss of self-tolerance along with autoreactive T and B cell activation resulting in generation of pathogenic autoantibodies leading to tissue injury (Choi et al. 2012). Patients affected with SLE had posed a serious concern during the COVID-19 pandemic as they are already susceptible to infections because of their immune system and the related organ damage in addition to ongoing immunosuppressive treatments (Ehrenfeld et al. 2020). However paradoxically, immunosuppressants were identified as a means of reducing inflammation and likelihood of acute respiratory distress syndrome (ARDS) in COVID-19 patients (Horisberger et al. 2020). While the anti-viral immunity is essential for protection against COVID-19, a hysterical pro-inflammatory cytokine storm may lead to damaging the lungs and other organs resulting in substantial increase in morbidity and mortality (Spihlman et al. 2020). Several cases of SLE patients have been reported of getting COVID-19 (Gartshteyn et al. 2020). However, reports of SLE manifestations after COVID-19 infections are limited. Zamani et al., have reported a case of 39 years old Persian male displaying SLE manifestations following SARS-CoV-2 infection, without any prior history of SLE (Zamani et al. 2021).

3.5.7 Type 1 Diabetes

Type 1 diabetes (T1D) is one of the most prevalent autoimmune disorders caused by combination of genetic and environmental triggers leading to immune mediated destruction of β-cells causing in lifelong dependency on exogenous insulin (Gan et al. 2012). Several viral infections such as coxsackievirus, cytomegalovirus and enterovirus, have been reported to be associated with T1D (Pak et al. 1988; Stene and Rewers 2012; Eizirik and Op de Beeck 2018). However, there is no clear spectrum of SARS-CoV-2 and T1D association and only a few studies have been reported which are needed to be interpreted carefully. A few studies have reported ketosis and induced diabetic ketoacidosis (DKA) in diabetic patients with SARS-CoV-2 infection; however, overall diabetic manifestations were not clear (Firouzabadi et al. 2020; Dehghani Firouzabadi et al. 2020). Some other studies have stated the development of diabetes and serious metabolic complications in COVID-19 patients (Chee et al. 2020; Heaney et al. 2020). Nevertheless, there are very scarce reports substantiating T1D and COVID-19 association and the possible reasons could be the younger age of T1D patients, lower prevalence of T1D, and

high numbers of $CD8^+$ T cells in T1D which may play a defensive role against SARS-COV2 infection (Chowdhury and Goswami 2020).

3.5.8 Vitiligo

Vitiligo is one of the most common pigmentary skin disorders characterized by circumscribed white patches in the skin resulting due to the autoimmune destruction of melanocytes from the epidermis (Dwivedi et al. 2013a; Bergqvist and Ezzedine 2020). The exact pathomechanism is not clear; however, it is proposed that oxidative stress might be an initial trigger generating endoplasmic reticulum (ER) stress which subsequently might instigate and exacerbate of anti-melanocyte immune response (Laddha et al. 2013; Jadeja et al. 2021). Both humoral and cell-mediated autoimmune responses have been found to be involved in melanocyte destruction (El-Gayyar et al. 2020; Giri et al. 2020a, b). Moreover, studies have suggested the role of IFN-γ and TNF-α cytokines in melanocytes destruction (Laddha et al. 2012; Dwivedi et al. 2013b; Harris 2015; Giri et al. 2021b). Unlike the other autoimmune disorders discussed in this chapter, there are not much evidence of association between vitiligo and COVID-19 to the best of our knowledge except one recent report by Herzum et al. (2022). They report a case of 45-year-old woman presented with well demarcated milky-white patches developed after 2 weeks of SARS-CoV-2 infection. On the follow up studies it was observed that the lesions were stabilized after 1 month of initial progression (Herzum et al. 2022). It is noteworthy that the protection against the viral infection and disease onset significantly rely on functional innate and adaptive immunity in addition to the interferon signaling pathways. Based on the fact that in generalized vitiligo (GV) there is a shift of the immune response towards adaptive type 1 (IFN-γ and $CD8^+$ T cells) and innate immune responses, it was speculated that patients with GV may clear SARS-CoV-2 infection more effectively and reduce the risk of COVID-19 development. However, this hypothesis needs to be validated by further studies in this direction (Post et al. 2021) (Table 3.2). On the other hand, other studies propose that in case of COVID-19, vitiligo autoimmunity may affect the cytokine storm-related disease burden. Moreover, study by Adlen and Henzy reported a significant difference in COVID-19 manifestations in patients with other autoimmune co-morbidity such as vitiligo (Aidlen and Henzy 2021).

3.5.9 Alopecia areata

Alopecia areata (AA) is an autoimmune dermatological condition wherein immune system attacks hair follicles, resulting in a non-scarring form of hair loss (Fukuyama et al. 2022). The predominance of AA accounted higher in patients aged 10–25 years (Juárez-Rendón et al. 2017). Pathogenesis of AA includes autoimmune response against hair follicles along with factors affecting our daily lifestyle (Minokawa et al. 2022). In AA, lymphocytic cells infiltrate around the peribulbar region of hair

follicles which results in patchy loss of hair follicles (Guo et al. 2015). COVID-19 emergence is reported to be associated with alopecia in infected patients, including some cases of AA. Different studies performed worldwide have reported both manifestation of new-onset AA and progression of pre-existing AA condition after SARS-CoV-2 infection. Patients between age of 13 and 56 years and without previous medical history of AA have shown new-onset AA with significant patchy hair loss on scalp. An observational study carried out using questionnaire included survey of 389 patients, which reported recurrence of AA in 44% patients following SARS-CoV-2 infection (Christensen and Jafferany 2022). However, a retrospective study including 32 patients with mild-to-moderate COVID-19 has given controversial data; which shows no acceleration of AA symptoms after 6 months of SARS-CoV-2 infection (Rudnicka et al. 2021). These studies suggest a complex relationship between AA and COVID-19 and requires further investigations to understand the association between COVID-19 and AA (Christensen and Jafferany 2022).

3.5.10 Cold Agglutinin Syndrome (CAS)

Cold agglutinin syndrome is another rare autoimmune hematological disorder, which accounts for 25% of all autoimmune hemolytic anemia (AIHA) cases. The autoantibodies, also known as cold agglutinins, agglutinate red blood cells (RBCs) at 4 °C. It is observed to be predominant in patients aged 51–96 years (Berentsen and Tjønnfjord 2012). Cold agglutination is described to be associated with viral infections including rubella virus, HIV, influenza viruses, varicella-zoster virus (VZV), and Epstein–Barr virus (EBV) (Kaur et al. 2021). After COVID-19 pandemic, cold agglutinin syndrome is also reported to be clinically important in SARS-CoV-2 infection as one of the hematological manifestations. In vivo hemolysis due to presence of cold agglutinins was diagnosed in two SARS-CoV-2 infected men. The antibodies reacted at cold body temperatures with RBCs of patient and donor. In these cases, refractory septic shock, hypoxic respiratory failure and progressive thrombocytopenia were developed during COVID-19 disease (Jensen et al. 2020). Other case-studies have also reported that following the SARS-CoV-2 infection, patients have developed CAS with low levels of hemoglobin, elevated levels of bilirubin and lactate dehydrogenase as well as abnormality in other blood parameters. These reports indicate that detection of the hemolytic patterns in SARS-CoV-2 infected patients and management of the severe disease complications are necessary (Patil et al. 2020; Maslov et al. 2020; Huscenot et al. 2020).

3.5.11 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS), also called “Hughes syndrome,” is a thrombo-inflammatory disorder, characterized by formation of blood clots in veins and arteries. Antiphospholipid autoantibodies (aPL), specifically anticardiolipin

antibodies (aCL), anti-β2 glycoprotein-I (β2GPI) antibodies, and lupus anticoagulant (LA) are considered as markers of APS (Cervera 2017). Antiphospholipid syndrome is found to be entangled with 33% cases of SLE (Knight and Kanthi 2022). In addition, APS is associated infections, drug and immune system related disease, and metastatic tumors. The frequency of antiphospholipid autoantibodies falls between 1% and 5% in population. Moreover, aPL crosslink with surface protein of platelets and endothelial cells, propelled by procoagulant and anticoagulant reactions, which further evolves to thromboembolic lesions (Cervera 2017). Evidences indicate that COVID-19 affects immune system and cardiovascular system, in additive manner to other multiorgan systemic disease. In a clinical investigation, serum samples of 29 patients with severe COVID-19 were tested. The study reported that 20 patients out of 29 exhibited presence of several systemic autoantibodies including antibodies against aCL (IgG/IgM), a-β2GPI (IgG/IgM), p-ANCA, and c-ANCA (Vlachoyiannopoulos et al. 2020). In another study of 56 COVID-19 cases, increased serum concentration of aCL was observed in severe COVID-19 patients compared to moderate infection, suggesting for risk of thromboembolic events (Bertin et al. 2020). Additionally, in study of 66 COVID-19 patients 47% exhibited positive result for IgA aCL (25.8%) and IgG aβ2GP1 (18.2%) (Xiao et al. 2020). These data revealed that circulating levels of aPLs are clinically important to understand development and severity of COVID-19 associated immunothrombosis.

3.6 Autoimmune Disease: A Risk Factor for Severe COVID-19?

Previous studies have suggested for development of autoimmune diseases after SARS-CoV-2 infection (Galeotti and Bayry 2020; Ehrenfeld et al. 2020; Cavalli et al. 2020; McMillan et al. 2021; Liu et al. 2021). However, the role of autoimmune disease in severe COVID-19 is controversial. Since the COVID-19 pandemic has begun, many autoimmune disease patients have suspended their therapies due to the fear of immune suppression. However, it might lead to worsening of autoimmune conditions (Liu et al. 2021). Therefore, a better understanding of the role of autoimmune diseases on COVID-19 development is required to improve COVID-19 and autoimmune disease management.

Initial studies had found that patients with autoimmune disease were not a risk factor for COVID-19 (Zen et al. 2020). However, multicentric study from China found that autoimmune disease patients may be at an increased risk of COVID-19 development (Zhong et al. 2020). Moreover, a Spanish study found that autoimmune disease patients might be at a greater risk for severe COVID-19 (Pablos et al. 2020). Additionally, patients with rheumatic inflammatory disease have been found to be at a greater risk towards development of severe pneumonia (Bachiller-Corral et al. 2021). Similarly, patients with autoantibodies against ACE2 and angiotensin type-1 receptors have been found to be at an increased risk for COVID-19 severity (Rodriguez-Perez et al. 2021). Recently, a meta-analysis study suggested that patients with autoimmune diseases had an increased risk of COVID-19 (Akiyama et al. 2021). Studies have also suggested for the presence of autoantibodies in severe

COVID-19 patients (Bastard et al. 2020; Zhou et al. 2020; Zuo et al. 2020; Vlachoyiannopoulos et al. 2020). Although the studies correlating COVID-19 in autoimmune patients are scarce, the findings suggest that autoimmunity might play a critical role in increasing COVID-19 severity.

3.7 Conclusions

COVID-19 pandemic has had significant global health impact. Similar to autoimmune diseases, COVID-19 manifestations causes immune system mediated tissue and organ damage. SARVS-CoV-2 infection leads to various autoimmune conditions like Guillain-Barre syndrome, Immune thrombocytopenic purpura, Kawasaki disease, Autoimmune thyroid diseases, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Type 1 Diabetes, Vitiligo, Alopecia areata, Cold agglutinin syndrome, Antiphospholipid syndrome through various mechanisms such as molecular mimicry, bystander activation, cytokine storm, production of autoantibodies, etc. Furthermore, studies have also suggested a correlation between autoimmune diseases and risk of developing severe COVID-19. However, future studies must investigate the relationship between severe COVID-19 and autoimmune diseases. Moreover, future studies must also investigate the genetic association between COVID-19 and autoimmune diseases. Additionally, the studies must characterize the risk for COVID-19 development in patients having pre-existing autoimmune diseases, which might be helpful in treatment and management of both COVID-19 and autoimmune disease patients.

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The Protective Discourse Between Infections and Autoimmunity

4

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Abstract

Autoimmune diseases are characterized by aberrant immune response against host own tissues. Studies have suggested that through molecular mimicry, bystander activation, and cross-reactivity, infections can trigger autoimmune diseases. However, paradoxically recent studies have highlighted the role of bacteria, viruses, and parasites in protection against autoimmune diseases. Epidemiological evidences and hygiene hypothesis also highlight the involvement of microbes in protection against autoimmune diseases. Interestingly, the data suggests increased incidence of the autoimmune diseases in developed countries. Microorganisms can protect against autoimmune diseases by antigenic competition, innate immune mechanisms, immune regulation; however, the detailed mechanisms underlying the involvement of microorganisms in protection of autoimmune diseases is unknown. The detailed understanding of mechanisms involved could lead to efficient therapeutics to treat autoimmune diseases.

Keywords

Autoimmunity · Antigenic competition · Innate immunity · Immune regulation · Infection

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4.1 Introduction

Autoimmune disease are chronic disorders characterized by loss of immune tolerance leading to aberrant immune response against hosts own tissues (Wang et al. 2015; Giri et al. 2022). The loss of immune tolerance leads to organ specific or systemic damage to the host (Janeway et al. 2001; Wang et al. 2015). Multiple factors like genetics, epigenetics, stress, environment, tobacco smoke, pharmaceutical agents, hormones, could trigger the development of autoimmune diseases (Costenbader et al. 2012). Moreover, recent studies suggest the role of infections in triggering autoimmune diseases (Arango et al. 2013). Conversely, studies have highlighted that infections can prevent or even suppress the development of autoimmune diseases (Arango et al. 2013).

According to the hygiene hypothesis, the decreased infections may lead to increase in the occurrence of allergies and autoimmune diseases (Sironi and Clerici 2010). The evidence for the hygiene hypothesis has been demonstrated worldwide (Bloomfield et al. 2006; Okada et al. 2010). Additionally, the animal model experiments have provided evidences for the hypothesis (Okada et al. 2010). Furthermore, studies suggest that the decreased rate of infections may be a likely explanation for increased incidence of autoimmune diseases in developed countries (Okada et al. 2010). Moreover, the prevalence of parasitic infections has been associated with increased risk of autoimmune disease (Strachan 2000; Arango et al. 2013). For example, the *Schistosoma mansoni* infection has been associated with protection of Type 1 diabetes mellitus (T1DM) (Cooke et al. 1999; Zaccone et al. 2003; Arango et al. 2013). Therefore, previous studies suggest that infections may be a potent immune system modulator (Arango et al. 2013).

However, the mechanism explaining the casual link between protective function of infection in development of autoimmunity is unclear. Various factors such as reduced regulatory T (Treg) cells activation, altered pro-inflammatory, and anti-inflammatory cytokine levels, changes in the microbiota may be linked with increased incidence of autoimmune diseases (Moudgil and Choubey 2011; Dwivedi et al. 2013a, 2015, 2017; Giri et al. 2020b, 2021a, 2022). Moreover, studies suggest that infections may suppress variety of autoimmune diseases by modulating immune response, non-specific to the particular pathogen (Sfriso et al. 2010). Given the role of infections in controlling aberrant immune response, this chapter focuses on the involvement of infections in protection of autoimmune diseases.

4.2 Autoimmune Diseases

Autoimmune diseases are characterized by loss of immune tolerance leading to destruction of bodies own tissues by self-reactive immune cells (Wang et al. 2015; Giri et al. 2022). The prevalence of autoimmune diseases is about 5% worldwide, and they represent a major concern of mortality and morbidity (Leslie and Hawa 1994; Wang et al. 2015). The autoimmune diseases are generally divided into two types organ specific autoimmunity, where the immune system mediated destruction

is localized to a particular organ, the other type in systemic autoimmunity, where multiple organs are involved (Janeway et al. 2001). Despite enormous research in the field there is no cure for most of the autoimmune diseases, and the current therapeutics mostly focus on symptomatic relief (Chandrashekara 2012).

The exact triggering factor is unknown but multiple factors such as environment, genetics, epigenetics, tobacco smoke, infections may be responsible for the triggering the development of autoimmune response (Giri et al. 2022). The initial trigger generally activates the innate immune cells, which leads to activation of antigen presenting cells (APCs) and increased production of pro-inflammatory cytokines (Gandhi et al. 2010; Thanapati et al. 2017; Giri et al. 2022). The activated APCs stimulate the adaptive immune response by activating self-reactive $CD4^+$ and $CD8^+$ T cells (Skapenko et al. 2005; Giri et al. 2022). The self-reactive $CD4^+$ T cells further aids in activating self-reactive $CD8^+$ T cells and B cells, which exacerbates the autoimmune response (Skapenko et al. 2005; Giri et al. 2022). Additionally, the self-reactive $CD4^+$ T cells mediate autoimmune response by FAS-FASL-mediated apoptosis (Tateyama et al. 2000; Giri et al. 2020b).

The self-reactive $CD8^+$ T cells are the major culprits of the autoimmune response that mediate autoimmunity by production of the cytotoxic granules like granzyme B and perforin, resulting in apoptosis of target cells (Janeway et al. 2001). Additionally, they exacerbate the tissue damage by production of pro-inflammatory cytokines and FAS-FASL mediated apoptosis (Tateyama et al. 2000; Giri et al. 2020b). Apart from this, autoreactive B cells produce autoantibodies, which are the hallmark of various autoimmune diseases like RA, MS, SLE, and T1DMM (Hampe 2012). The autoantibodies after binding to the cellular receptors mediate cell lysis through complement activation and antibody-dependent cellular toxicity (Hampe 2012).

The subset of $CD4^+$ T cells known as regulatory T cells (Tregs), maintains immune tolerance by suppressing such self-reactive T and B cells (Dwivedi et al. 2013a, 2015; Giri et al. 2020a, 2021c). However, studies suggest that the decreased expression of FOXP3 (the master regulator of Tregs), leads to quantitate and functional Tregs defects in various autoimmune diseases (Long and Buckner 2011; Dwivedi et al. 2013b; Giri et al. 2020a, b). Overall, the initial trigger of autoimmune response and failure of immunological tolerance leads to widespread activation of self-reactive T and B cells contributing to pathogenesis of autoimmune diseases (Giri et al. 2022).

4.3 Proposed Mechanisms for Protective Effect of Infections on Autoimmune Diseases

Compelling evidence suggest correlation between decreased incidence of infections and increase in occurrence of autoimmune diseases and allergies in developed north American and European countries (Gale 2002; Mayr et al. 2003; Joner et al. 2004; Zaccone et al. 2006; Okada et al. 2010). There is an increase in the development of T1DM and multiple sclerosis for the past decade in the Western countries (Bach 2009; Okada et al. 2010). Such trend is not observed in less developed countries.

Moreover, such high incidence cannot be attributed solely to genetic factors since such increased autoimmune disease incidence have also been observed in immigrated families (Detels et al. 1972; Leibowitz et al. 1973; Bodansky et al. 1992; Symmons 1995; Staines et al. 1997; Hammond et al. 2000; Okada et al. 2010). The mechanism of protective effect mediated by infections on autoimmune diseases is multifactorial (Okada et al. 2010). Here, we discuss certain mechanisms like antigenic competition, innate immune mechanisms, immune regulation, mediated by infections which could lead to protection against autoimmune diseases.

4.3.1 Antigenic Competition

Antigenic competition is defined by diminished immune response to one antigen in the presence of another antigen (Pross and Eidinger 1974; Liacopoulos and Ben-Efraim 1975; Bach 2001). It occurs between closely related and unrelated antigens (Fujinami and Oldstone 1989; Oldstone 1998; Bach 2001). The phenomena are well studied in multicomponent vaccines such as diphtheria–pertussis–tetanus (DPT), and *Haemophilus influenzae*-tetanus vaccines (Table 4.1) (Halperin et al. 1999; Jatana and Nair 2007). Additionally, envelope component of human immunodeficiency virus (HIV) vaccine leads to reduced $CD4^+$ T cells response against Gag/Pol antigens due to antigenic competition (Table 4.1) (Kallas et al. 2019). Moreover, similar phenomena have been observed in case of influenza virus, where the antigenic competition leads to increased immune response against hemagglutinin and decreased immune response against neuraminidase (Table 4.1) (Johansson 1988). This antigenic competition may be due to presence of multiple components or multiple antigens (Bach 2001). In some cases, the antigenic competition could lead to one antigen being dominated and other being suppressed or in other cases both the antigens can be mutually suppressed (Bach 2001).

In the cases of autoimmune diseases, the infections can lead to increased competition with self-antigens, which could result in suppressed autoimmune response (Hara and Iwasa 2020). For example, administration of *Streptococcal* and *Klebsiella* extracts significantly reduces diabetes in non-obese diabetic (NOD) mice (Toyota et al. 1986; Saï and Rivereau 1996). Moreover, the immunization against bovine serum albumin (BSA) drastically reduces thyroiditis (McMaster and Kyriakos 1970). There may be multiple underlying mechanisms through which these infections can induce antigenic competition. The activation of adaptive immune response is triggered by antigen presenting cells (APCs). The APCs through the process of phagocytosis present the antigens on their surface (Janeway et al. 2001). These phagocytosis and subsequent antigen presentation process could be subject to saturation (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Moreover, Fc receptors may also be saturated due to presence of antibodies against particular pathogens (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Furthermore, evidences suggest the major histocompatibility complex (MHC) may be saturated by the presence of foreign antigens (Fig. 4.1) (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001). Thus, the presence of infectious pathogen through antigenic

Table 4.1 Mechanisms involved for beneficial role of infections in suppression of autoimmune diseases

Mechanism	Description/example	Reference
Antigenic competition	Immune response to one antigen leads to diminished immune response against another antigen.	Chatenoud et al. (1986), Babbitt et al. (1986), Johansson (1988), Adorini et al. (1988), Fujinami and Oldstone (1989), Adorini (1998), Oldstone (1998), Halperin et al. (1999), Bach (2001, 2005), Jatana and Nair (2007), Gaisford and Cooke (2009), Kallas et al. (2019)
	Presence of multiple components or multiple antigens can lead to saturation of antigen presentation and B cell antibody production.	
	Specific antibodies against pathogens can be more immunodominant compared to antibodies against self-antigens.	
	Pathogen specific T cells can compete with self-reactive T cells, by consumption of IL-2.	
	Response against pathogen can trigger regulatory T cells which could suppress self-reactive T and B cells.	
	HIV envelope protein reduces $CD4^+$ T cells response against Gag/Pol antigens.	
	In influenza virus infection, immune response against hemagglutinin reduces immune response against neuraminidase.	
	Multicomponent vaccines such as DPT vaccine, and *Haemophilus influenzae*-tetanus vaccine.	
Innate immune mechanisms	Infections can modulate the immune response by binding to various TLRs leading to production of vast array of cytokines including regulatory cytokines.	Zaccone et al. (2003), Bach (2005), Lang et al. (2005), Bartemes and Kita (2018)
	TLR-dependent production of IL-10 and TGF-β are crucial in regulation of autoimmunity.	
	Binding of fungi to TLR2 activates Th2 type response.	
	Soluble antigens of worm induce NKT cells which inhibit T1DM.	
	Staphylococcal enterotoxin B can suppress experimental allergic encephalomyelitis and collagen-induced arthritis by inhibiting Vβ-T cell subsets.	

(continued)

Table 4.1 (continued)

Mechanism	Description/example	Reference
Infections induced Immunoregulation	Tregs activated against antigens can suppress the autoimmune response.	Bach (2001, 2005), Alyanakian et al. (2006), Raine et al. (2006), Lee et al. (2008), Gaisford and Cooke (2009), McSorley and Maizels (2012)
	Helminths can recruit Tregs by activating IL-10, IL-13, and TGF-β.	
	Mycobacterial infections control autoreactive T cells trafficking in MS and T1DM.	
	Extract of Gram-positive bacteria can enhance TGF-β production resulting in suppression of T1DM.	
	Viruses such as LCMV and HIV infect immune cells, leading to depletion of the host immune response.	
	Viral infections can trigger IFN-β, an immunoregulatory cytokine.	

DPT vaccine diphtheria–pertussis–tetanus vaccine, *TLR* toll like receptor, *Tregs* regulatory T cells, *TGF-β* transforming growth factor-β, *T1DM* type 1 diabetes, *LCMV* lymphocytic choriomeningitis virus, *HIV* human immunodeficiency virus, *IFN-β* interferon-β

competition could lead to reduced immune response against self-antigens contributing to decreased autoimmunity (Babbitt et al. 1986; Adorini et al. 1988; Bach 2001).

Furthermore, B cells also act as APCs, and the complex procedure of processing antigens, B cell differentiation, proliferation, and antibody production could lead to antigenic competition through various mechanisms (Bach 2001). The antibody directed towards the pathogen could be more immunodominant compared to self-antigens: as it may be present in a relatively higher numbers or it may have high affinity and avidity. Moreover, B cells precursors could be present in higher numbers for the particular antigen (Adorini 1998; Bach 2001, 2005; Gaisford and Cooke 2009). Thus, the antigenic competition mediated antibody against pathogen could lead to reduced autoimmune response.

Apart from this, restriction of the activated $CD4^+$ T cells' number could also influence B cells help. The presence of pre-existing pathogen specific T cells could interfere in activation of self-reactive T cells by consumption of IL-2 (Chatenoud et al. 1986; Bach 2001). Moreover, closely related antigens can act as T cells antagonist and can inhibit the activation of T cells specific to self-antigens (Fig. 4.1) (Chatenoud et al. 1986; Bach 2001). Furthermore, immune responses against pathogens could induce Treg cells which could suppress self-reactive T and B cells (Fig. 4.1) (Bach 2001). Thus, the decreased activation of self-reactive $CD4^+$ T cells could contribute to reduced activation of self-reactive B and cytotoxic T cells leading to decreased autoimmune response.

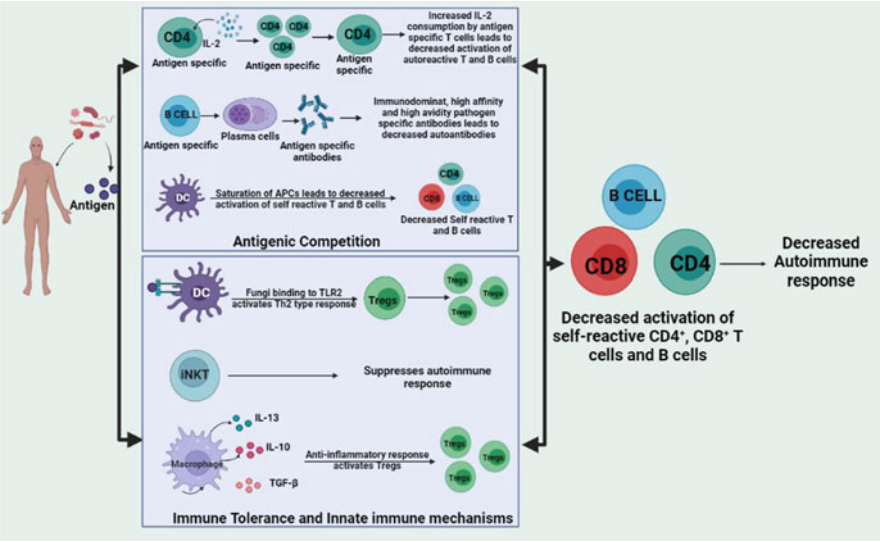

Fig. 4.1 Proposed mechanism for the beneficial role of infections in protection towards autoimmune diseases. Increased consumption of IL-2 by pathogen specific T cells, can lead to reduced activation of self-reactive $CD4^+$ T cells, which could contribute to reduced activation of self-reactive B and cytotoxic T cells leading to decreased autoimmune response. Additionally, pathogen specific antibodies can be more immunodominant compared to autoantibodies. Moreover, saturation of antigen presentation process and antibody production can lead to decreased self-reactive T and B cells response. Apart from this, the binding of fungi to TLR-2 promotes Th2 response. Additionally, soluble antigens of worm induce NKT cells which inhibit autoimmune response. Furthermore, helminths activate a subset of macrophage that produce anti-inflammatory cytokines like IL-10, IL-13, and TGF-β, which recruit Tregs. Overall pathogens through antigen competition, innate immune mechanisms and immune tolerance suppress autoimmune response

4.3.2 Innate Immune Mechanisms

Autoimmune diseases are characterized by specific adaptive immune response against the host cells; however, the role of innate immune response cannot be denied in autoimmune diseases (Waldner 2009). Specifically, studies have suggested the involvement of toll like receptors (TLRs) in development of autoimmune response, in RIP-LCMV mice where, TLR3 binding and subsequent IFN-α production is crucial in development of autoimmunity (Bach 2005; Lincez et al. 2021). However, in vivo and in vitro studies have suggested that TLR-dependent production of IL-10 and TGF-β are crucial in regulation of autoimmunity (Table 4.1) (Bach 2005; Lang et al. 2005).

Microbial infections, and commensal bacteria can modulate the immune response by binding to various TLRs (Fig. 4.1) (Bach 2005). The binding of pathogens to the TLRs could lead to production of vast array of cytokines which could include regulatory cytokines (Bach 2005). For example, the binding of fungi to TLR2 could activate Th2 type response (Table 4.1, Fig. 4.1) (Bartemes and Kita 2018).

Moreover, fungi can regulate the inflammatory response through activating Tregs and production of anti-inflammatory cytokines (Table 4.1) (Bartemes and Kita 2018). This could lead to suppression of self-reactive T and B cells leading to reduced autoimmune response. Moreover, they are known to induce Treg cells by binding to TLR2 on dendritic cells (DCs) (Fig. 4.1) (Van der Kleij et al. 2002; Oliveira-Nascimento et al. 2012). Additionally, soluble antigens of worm induce NKT cells which inhibit T1DM (Fig. 4.1) (Zaccone et al. 2003). Moreover, superantigens such as *Staphylococcal* enterotoxin B are known to suppress the pathogenesis of experimental allergic encephalomyelitis and collagen-induced arthritis by inhibiting Vβ T cell subsets (Prabhu Das et al. 1996; Bach 2001). Overall, these studies highlight the importance of innate immune mechanisms in suppression of autoimmunity.

4.3.3 Infections Induced Immunoregulation

The suppressive effect induced against a particular antigen could through bystander activation suppress the autoimmune response (Bach 2005). Therefore, the Treg cells activated in response to the particular antigen could in turn dampen the autoimmune response (Bach 2005). The mechanisms involved could be by enhancement of Th2 cells which could suppress the inflammatory response leading to protection against autoimmune diseases (Table 4.1).

Experimental evidence suggests that administration of gram-positive bacterial extract in NOD mice enhances the anti-inflammatory cytokine TGF-β production resulting in suppression of T1DM (Alyanakian et al. 2006). Furthermore, helminths activate a subset of macrophage that produce anti-inflammatory cytokines like IL-10, IL-13, and TGF-β, which recruit Tregs (Fig. 4.1) (McSorley and Maizels 2012). Furthermore, in MS, mycobacterial infections control trafficking of autoreactive T cells (Lee et al. 2008; Gaisford and Cooke 2009). Moreover, in T1DM the *Salmonella typhimurium* infection has been linked with inhibition of trafficking of autoreactive T cells trafficking to pancreas (Table 4.1) (Raine et al. 2006; Gaisford and Cooke 2009).

Several viruses have tropism towards immune cells and viral infections such as LCMV could infect the immune cells (Zinkernagel et al. 1999; Bach 2001). This could lead to reduction in autoreactive immune cells, resulting in suppression of autoimmune responses (Bach 2001). The most evident case of infection induced immunosuppression is of human immunodeficiency virus, which is known to infect $CD4^+$ T cells, leading to depletion of the host immune response (Bach 2001). Moreover, viral infections could lead to increased production of IFN-β, an immunoregulatory cytokine (Bach 2001). Additionally, the IFN-β immunomodulatory properties have been used in the treatment of multiple sclerosis (Bach 2001). Interestingly a study has highlighted that lymphocytic choriomeningitis virus (LCMV) infection in diabetic NOD mice, delayed the onset of disease (Oldstone et al. 1990; Bach 2001). This could be due to suppression of $CD8^+$ T cells by TGF-β producing Treg cells.

Overall, the studies suggest microorganisms and viruses could suppress the ongoing autoimmune diseases by suppressing pro-inflammatory Th1 response and promoting anti-inflammatory Th2 response (Fig. 4.1) (Bach 2001, 2005; Gaisford and Cooke 2009). However, detailed mechanistic studies assessing how microbes regulate the autoimmune response can lead novel therapeutics for autoimmune diseases. Additionally, studies will highlight the complex interactions between microbes and cellular signaling pathways involved in development of autoimmunity.

4.4 Epidemiological Evidence for the Protective Role of Infections in Human Autoimmune Diseases

Incidence of autoimmune diseases including MS, RA, T1DM have increased dramatically over the past few decades (Poser et al. 1989; Green and Patterson 2001; Myasoedova et al. 2010). Furthermore, this increased incidence has been observed prominently in the developed countries (Bach 2001). Epidemiological data suggests the increased incidence of MS, T1DM and Crohn's diseases in North America and Europe (Bauer 1987; Bach 1994; Kurtzke 1995; Green and Patterson 2001). The increased incidence cannot be solely linked with genetics (Okada et al. 2010). Interestingly recent evidence has suggested changes in lifestyle in the developed countries could lead to increased occurrence of allergic and autoimmune diseases (Okada et al. 2010). Moreover, according to the hygiene hypothesis the decreasing incidence of infections in developed countries could lead to increased incidence of allergic and autoimmune diseases (Okada et al. 2010). The hygiene hypothesis is supported by the fact that the autoimmune diseases have increased in immigrants from low income countries to developed countries (Okada et al. 2010).

In developing countries, the incidence of asthma, allergic rhinitis and atopic dermatitis has increased by over 15% in United Kingdom, New Zealand, and Australia (Okada et al. 2010). Moreover, there is an increased prevalence of autoimmune diseases such T1DM in European countries such as Finland (Harjutsalo et al. 2008). Furthermore, the prevalence of inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis (Bach 2002) and primary biliary cirrhosis (Rautiainen et al. 2007), has increased. Interestingly, the incidence of T1DM and MS has also increased in the Asian and African immigrants in the US (Detels et al. 1972; Staines et al. 1997).

Multiple factors could explain the increased incidence of autoimmune diseases. Recent studies suggest the change in the microbiota and decreased exposure to infections in childhood could lead to autoimmune diseases, by multiple mechanisms like decreased immune regulation, antigenic completion and innate immune factors (Bach 2001, 2005; Gaisford and Cooke 2009). Moreover, studies suggest that increased exposure to farming and cowsheds in early life could prevent atopic diseases (Riedler et al. 2001; Ege et al. 2006). Moreover, exposure to endotoxin in the childhood protects against asthma and atopy (Braun-Fahrländer et al. 2002). Furthermore, *Schistosoma* infections have also been reported to protect against atopy (Flohr et al. 2006; Okada et al. 2010). Therefore, the detailed understanding of the

role of microorganisms could lead to potent therapeutics for treatment of autoimmune diseases.

4.5 Animal Model Studies for Exploring the Protective Effects of Infections on Autoimmune Diseases

Studies have suggested a strong correlation between infections and incidence of autoimmunity (Okada et al. 2010). Here, we discuss few animal model studies which suggest the role of infections towards protection of autoimmune diseases.

4.5.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by loss of insulin producing β-cells (Hara et al. 2013). The exact etiology is unknown, but multiple factors like genetics, autoimmunity, and environmental factors can trigger T1DM. Insulitis and elevated autoantibodies produced against β-cells lead to β-cell death (Pihoker et al. 2005). The destruction of β-cell death leads to symptoms like urination, loss of appetite, fatigue, thirst, and hyperglycaemia (Pihoker et al. 2005).

Although microorganisms are thought to be triggering factors for development of autoimmune diseases, but animal model studies suggest that T1DM is associated with sanitary conditions of animal facilities (Bach 2002). The studies suggest that lower the burden of infection, the higher the incidence of diabetes (Like et al. 1991; Okada et al. 2010). Moreover, infection of NOD mice with bacteria, viruses, and parasites prevents NOD mice from diabetes (Table 4.2) (Bach 2002). Apart from this, probiotics and microbial components also protect NOD mice from diabetes (Petrovsky 2010; Kim et al. 2020). Additionally, exposure to components like soluble worm antigen and soluble egg antigen from *Shistosoma mansoni*, OM89 and OM85 from *Escherichia coli* and ES62 from *Acanthocheilonema viteae* can protect from autoimmune diseases like T1DM, SLE, and RA (Zaccone et al. 2003; Alyanakian et al. 2006; Harnett and Harnett 2006; Toussirot et al. 2006; Gaisford and Cooke 2009).

Additionally, administration with complete Freund's adjuvant (CFA) in NOD mice has shown to protect from T1DM (Qin et al. 1993). Similarly, *Mycobacterium bovis* and *Mycobacterium avium* have shown to suppress autoimmune diabetes (Brás and Águas 1996; Inafuku et al. 2015). Interestingly, infection with viruses such as LCMV, murine hepatitis virus and LDV and *Schistosoma mansoni* parasites have shown to suppress T1DM in NOD mice (Oldstone et al. 1990; Wilberz et al. 1991; Takei et al. 1992; Bach 2002; Zaccone et al. 2009). Moreover, *Pseudomonas aeruginosa* signaling molecule, *N*-(3-oxododecanoyl)-L-homoserine lactone suppresses insulitis and controls T1DM in NOD mice (Pritchard et al. 2005). Additionally, *Salmonella typhimurium* infection generates immunomodulatory DCs which suppress T1DM in NOD mice (Raine et al. 2006). Moreover,

Table 4.2 Protective role of infections in autoimmune disorders

Autoimmune disease	Infection	Reference
Type 1 diabetes mellitus	*Mycobacterium bovis* and *Mycobacterium avium* suppresses autoimmune diabetes.	Toyota et al. (1986), Oldstone et al. (1990), Wilberz et al. (1991), Takei et al. (1992), Brás and Águas (1996), Saï and Rivereau (1996), Bach (2002), Zaccone et al. (2003), Pritchard et al. (2005), Alyanakian et al. (2006), Raine et al. (2006), Saunders et al. (2007), Zaccone et al. (2009), Petrovsky (2010), Inafuku et al. (2015), Kim et al. (2020)
	Pseudomonas aeruginosa signaling molecule, *N*-(3-oxododecanoyl)-L-homoserine lactone suppresses insulitis and T1DM in NOD mice.	
	Salmonella typhimurium induces immunomodulatory DCs, thereby suppressing diabetes in NOD mice.	
	Streptococcal and *Klebsiella* extracts suppress diabetes in NOD mice.	
	Gram-positive bacterial extract enhances TGF-β production resulting in suppression of T1DM.	
	LCMV, murine hepatitis virus and LDV protect against diabetes in NOD mice.	
	Trichinella spiralis and *Heligmosomoides polygyrus* helminths suppress autoimmune diabetes.	
	Soluble worm antigen and soluble egg antigen from *Shistosoma mansoni* can protect against diabetes.	
	Probiotics and microbial components also protect NOD mice from diabetes.	
	Bacteria, viruses, and parasites infection prevents NOD mice from diabetes.	
Rheumatoid arthritis	Bacteria and parasite infections can suppress arthirits.	Pearson and Taylor (1975), Toussirot et al. (2006), Harnett et al. (2008), Osada et al. (2009), Shi et al. (2011)
	S. mansoni can decrease autoantibodies and pro-inflammatory cytokine production in CIA.	
	E. coli extract suppresses arthritis.	
	Symphacia obvelata parasites suppress CFA arthritis is rats.	
	Acanthocheilonema viteae suppresses CIA.	
	Hymenolepis diminuta reduces CFA.	
	Bacterial extract OM-89 induce IL-10 production and suppress pro-inflammatory cytokine in RA.	

(continued)

Table 4.2 (continued)

Autoimmune disease	Infection	Reference
Multiple sclerosis	Bacterial and Helminths' infections protect against autoimmune MS in EAE model.	Lehmann and Ben-Nun (1992), Sewell et al. (2003), La Flamme et al. (2003), Gruden-Movsesijan et al. (2008), Walsh et al. (2009), Cleenewerk et al. (2020), White et al. (2020)
	S. mansoni converts Th1/Th17 response to anti-inflammatory Th2 response, thus protecting from EAE.	
	Heligmosomoides polygyrus infection protects from EAE in IL-4Rα-dependent manner.	
	Fasciola hepatica infections control EAE through TGF-β-Mediated suppression of Th17 and Th1 responses.	
	Schistosomiasis parasitic infection reduces CNS inflammation thereby suppressing EAE.	
	Trichinella spiralis infection ameliorates the EAE in dose dependent manner in Dark Agouti rats.	
	Mycobacteria infection can prevent mice from EAE.	
	Mycobacterium bovis BCG diverts self-reactive T cells from CNS in EAE.	
	Mycobacterium tuberculosis exposure protects from EAE-susceptible mice from disease.	
	Bordetella pertussis protects mice from EAE.	
	Escherichia coli, *Shigella*, and *Staphylococcus aureus* infections suppress EAE.	
Inflammatory bowel disease	Helminth's infection suppresses IBD pathology.	Khan et al. (2002), Elliott et al. (2003, 2004), Summers et al. (2005a, b), Ruyssers et al. (2008), Motomura et al. (2009), Johnston et al. (2010), McSorley and Maizels (2012), Cleenewerk et al. (2020)
	S. mansoni infection suppress IBD by macrophage and IL-10 dependent mechanism.	
	Schistosome egg, suppresses pro-inflammatory cytokines production and enhances anti-inflammatory cytokines like IL-10 and TGF-β, thereby protecting from colitis.	
	Heligmosomoides polygyrus reduces colitis in IL-10 deficient manner.	

(continued)

Table 4.2 (continued)

Autoimmune disease	Infection	Reference
	Hymenolepis diminuta infections suppress colitis pathology by suppressing macrophage activation.	
	Trichuris suis improves disease activity index of ulcerative colitis.	
	Trichuris suis controls Crohn's disease.	
	Ancylostoma hookworm products suppress colitis.	
	T. spiralis infections and antigens suppress colitis pathology.	

T1DM type 1 diabetes *NOD mice* non-obese diabetic mice, *DCs* dendritic cells, *MS* multiple sclerosis, *IL-4Rα* interleukin-4 receptor α *BCG* Bacillus Calmatte-Gurin, *CIA* collagen-induced arthritis, *CFA* complete Freund's adjuvant, *LCMV* lymphocytic choriomeningitis virus, *LDV* lactate dehydrogenase-elevating virus, *EAE* experimental autoimmune encephalomyelitis, *IBD* inflammatory bowel disease, *CNS* central nervous system

gastrointestinal helminths such as *Trichinella spiralis* and *Heligmosomoides polygyrus* inhibit autoimmune diabetes in NOD mice (Saunders et al. 2007).

Although the data suggests the involvement of infections in protection against T1DM; however, the data is currently limited to animal model of diabetes (Bach 2001; Gaisford and Cooke 2009). Moreover, the underlying mechanisms how infections could suppress such autoimmune response is unknown. Infections and microbial components through antigenic competition, innate immune factors, immunoregulation could suppress the pro-inflammatory environment, promote anti-inflammatory cytokines and induce Treg cells, which could control the ongoing autoimmune response (Fig. 4.1) (Bach 2001, 2005; Gaisford and Cooke 2009). However, future animal model studies must explore the underlying mechanisms which could lead to development of potent therapeutics for treatment of T1DM.

4.5.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease, characterized by chronic joint inflammation leading to bone and cartilage damage. RA is responsible for significant morbidity as it causes disability, discomfort, stiffness, and decreased life expectancy (Thanapati et al. 2017; Carbone et al. 2020; Giri et al. 2021b). Although the exact etiology for RA is unknown, multiple factors such as genetics, autoimmunity, environment, diet alcohol, and smoking can trigger RA development (Giri et al. 2022). Although infections are considered to trigger autoimmune RA (Mahajna et al. 2015); however, recent evidence in animal model studies suggests that infections can protect from RA (Table 4.2) (Vischer 1993).

Evidence for pathogen induced RA protection are found in type II collagen-induced arthritis (CIA) arthritis model (Harnett et al. 2008). Studies suggests *Syphacia obvelata* parasite's infection suppresses CFA arthritis in rats (Pearson and Taylor 1975). Moreover, *S. mansoni* infections reduces autoantibodies and pro-inflammatory cytokine production in CIA arthritis models (Osada et al. 2009). Additionally, tapeworm, *Hymenolepis diminuta* infections in rats induces IL-10 dependent CFA arthritis (Shi et al. 2011). Overall, animal model studies suggest parasite infections can alleviate arthritis pathology by suppressing pro-inflammatory cytokine production and inducing anti-inflammatory cytokine production (McSorley and Maizels 2012). Additionally, bacterial extract OM-89 showed inhibition of arthritis by inducing IL-10 production and suppressing pro-inflammatory cytokine production in RA patients (Toussirot et al. 2006). The above mentioned studies suggest that bacterial and parasitic infections can protect from ongoing autoimmunity in RA by promoting anti-inflammatory response and suppressing pro-inflammatory response. However, future in vitro and in vivo studies are warranted to understand the underlying mechanism for development of potent therapeutics for treatment of RA.

4.5.3 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune neurological disease, characterized by chronic inflammation and demyelination resulting in symptoms such as vision loss, cognitive defects, depression, and bowel defects (Filippi et al. 2018). The pathogenesis of MS is due to autoimmune reactions against myelin proteins and gangliosides (Prat and Martin 2002). Multiple factors such as vitamin D deficiency, intestinal dysbiosis, viral infections, a hypercaloric diet, genetics, and environmental factors can trigger MS development (Milo and Kahana 2010). Although infections, particularly viral infections are considered to trigger MS development, but animal model studies suggest certain bacterial and helminth infection can protect against autoimmune MS (Table 4.2) (Sewell et al. 2003; La Flamme et al. 2003).

Several bacterial and parasitic infections have shown disease protection in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS (Lehmann and Ben-Nun 1992; Sewell et al. 2003; La Flamme et al. 2003; Gruden-Movsesijan et al. 2008). Studies suggest *Mycobacteria* infection can prevent mice from EAE (Lehmann and Ben-Nun 1992; Sewell et al. 2003). *Mycobacterium bovis* BCG diverts self-reactive T cells away from the central nervous system (CNS) which then suppresses EAE in mice (Sewell et al. 2003). Moreover, *Mycobacterium tuberculosis* exposure protects EAE-susceptible mice against induction of disease (Lehmann and Ben-Nun 1992). Moreover, *Bordetella pertussis* could also protect mice from EAE development (Lehmann and Ben-Nun 1992). Additionally, *Escherichia coli*, *Shigella*, and *Staphylococcus aureus* were found to be effective in suppressing EAE (Lehmann and Ben-Nun 1992). Moreover, *S. mansoni* parasite has shown to alleviate the EAE pathology (Cleenewerk et al. 2020). It converts the pro-inflammatory Th1/Th17 response to anti-inflammatory Th2 response

(Cleenewerk et al. 2020). Interestingly, *Heligmosomoides polygyrus* infection suppressed the EAE in IL-4Rα-dependent manner (White et al. 2020). *Fasciola hepatica* infections has been shown to control EAE through TGF-β-Mediated suppression of Th17 and Th1 responses (Walsh et al. 2009). Additionally, Schistosomiasis (a parasitic infection) reduces the inflammation in the CNS, thereby alleviating the EAE pathology (La Flamme et al. 2003). *Trichinella spiralis* infection also showed to ameliorate the clinical course of EAE in dose dependent manner in Dark Agouti rats (Gruden-Movsesijan et al. 2008).

Overall, the above mentioned studies suggest that bacterial and parasitic infections can control EAE; however, studies in this field are scarce and only limited to animal models of MS. Therefore, future in vitro and in vivo studies must be carried to identify the exact underlying mechanism to explore the role of infections in protection of MS, which will aid in the development of potent therapeutics for treatment of MS.

4.5.4 Inflammatory Bowel Disease (IBD)

Crohn's disease and ulcerative colitis are two main inflammatory bowel diseases (Seyedian et al. 2019). They are characterized by chronic inflammation in the digestive tract (Seyedian et al. 2019). The condition ulcerative colitis is characterized by chronic inflammation in the colon and rectum. Crohn's disease involves chronic inflammation in the lining of digestive tract (Seyedian et al. 2019). IBD is generally characterized by diarrhea, rectal bleeding fatigue, weight loss, abdominal pain, and cramping (Seyedian et al. 2019).

In mouse model of IBD, helminths' infections have been demonstrated to suppress disease pathology (Summers et al. 2005a, b; McSorley and Maizels 2012). For instance, *S. mansoni* infection suppressed the IBD by macrophage and IL-10 dependent mechanisms (Cleenewerk et al. 2020). Additionally, *Ancylostoma* hookworm products' administration suppressed the colitis (Ruyssers et al. 2008). *T. spiralis* infections and antigens also suppressed the colitis pathology (Khan et al. 2002; Motomura et al. 2009). Moreover, *Schistosome* egg has been shown to protect colitis by suppressing the production of pro-inflammatory cytokines as well as by inducing anti-inflammatory cytokines such as IL-10 and TGF-β (Elliott et al. 2003; McSorley and Maizels 2012). Moreover, *Heligmosomoides polygyrus* was demonstrated to dampen the colitis in an IL-10 deficient manner (Elliott et al. 2004). The *Hymenolepis diminuta* infections were also able to suppress colitis pathology by suppressing macrophage activation (Johnston et al. 2010), increased IL-10 and Tregs' production (Johnston et al. 2010; McSorley and Maizels 2012). Additionally, *Trichuris suis* improved the disease activity index of ulcerative colitis (Summers et al. 2005b). Furthermore, *Trichuris suis* was also shown to control Crohn's disease (Summers et al. 2005a).

The suppressive effects of the infections on IBD are not characterized well. However, the findings suggest that the infections suppress the ongoing infections by promoting the production of anti-inflammatory cytokines like IL-10 and TGF-β

(McSorley and Maizels 2012). Additionally it induces Tregs and suppresses Th1/Th17 associated cytokines after infection (McSorley and Maizels 2012). Thus, as shown in animal models of IBD the anti-inflammatory environment induced by infections can further lead to development of potent therapeutic strategies for IBD.

4.6 Conclusions

Infections are one of the major players which modulate the development of autoimmune diseases. Recently, compelling evidences have suggested the role of infections in protection of autoimmune diseases. However, the detailed underlying mechanisms how the infection could protect against autoimmune and allergic diseases are unclear. Therefore, in vitro and in vivo approaches studying the role of infections in suppression of autoimmune diseases are warranted. Moreover, considering ethical limitations for using infections in treatment of human autoimmune diseases, the therapeutic potentials of bacterial extracts in experimental models of autoimmune diseases must be investigated. Overall, a far better understanding for the underlying mechanisms for role of infections in protection of autoimmune diseases could pave a way to novel therapeutics for the treatment of autoimmune diseases.

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Part II

Microorganisms in Pathogenesis and Management of Autoimmune Kidney Diseases and Adrenal Insufficiency

5 Microorganisms in Pathogenesis and Management of IgA Vasculitis and IgA Nephropathy

Firdosh Shah and Mitesh Kumar Dwivedi

Abstract

IgA vasculitis is an autoimmune disease characterized by leukocyte infiltration into blood vessels. Infectious agents such as bacteria and viruses have been found in blood vessels. Despite several research studies, the link between infection and vasculitis remains unknown, probably due to a lack of suitable animal models and technical constraints in the pathogen detection. Moreover, microbial infections have been implicated in the etiology of IgA nephropathy. However, how the microbes participate in the infection process remains a subject of debate. Studies indicate that alteration in gut microbiome can contribute to progression of IgA nephropathy. This chapter discusses the involvement of microorganisms in IgA vasculitis and IgA nephropathy pathogenesis and portrays several findings that focus on the therapeutic aspects of these diseases.

Keywords

IgA vasculitis · IgA nephropathy · Gut microbiota · Short chain fatty acids (SCFAs) · Fecal microbiota transplantation (FMT)

5.1 Introduction

Vasculitis is an autoimmune disease marked by the presence of inflammatory leukocytes in blood vessels, leading to destructive damage to mural structures (Jennette et al. 2012). Vasculitis can be categorized into three categories based on the size, kind, and location of the afflicted vessels: Immunoglobulin A (IgA)

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vasculitis affects small vessels, while Kawasaki disease (KD) and polyarteritis nodosa (PAN) affect medium vessels, and Giant cell arteritis (GCA) and Takayasu arteritis (TA) affect large vessels (Jennette et al. 2012). Vasculitis pathophysiology is unknown, and the majority of vasculitis-related illnesses are considered idiopathic (Fiorentino 2003). Human and animal research, on the other hand, indicate the significance of microbiota in vasculitis which include viruses, bacteria, and parasites. The COVID-19 pandemic has recently sparked unexpected interest in infection-related inflammatory autoimmune disorders, such as IgA vasculitis. Children have been found to have vasculitis-like inflammatory signs with KD-like clinical symptoms. This medical condition was linked to exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and manifested in children as multisystem inflammatory syndrome (Feldstein et al. 2020).

Immunoglobulin A (IgA) nephropathy, an autoimmune disorder, is marked by deposition of polymeric and hypogalactosylated IgA1 in renal mesangium (Hastings et al. 2010; Moldoveanu et al. 2007). IgA nephropathy is one of the most frequent types of primary glomerulonephritis, affecting adults between the ages of 20 and 40 years (Schena and Nistor 2018). According to research, 20–40% patients with IgA nephropathy develop renal disease by 20 years of age (D'Amico 2004). Despite advances in our understanding of the pathogenesis of the disease and treatment, IgA nephropathy still remains a leading cause of mortality and morbidity. Currently, invasive kidney biopsy and renin-angiotensin system (RAS) inhibitors are used to confirm the diagnosis of IgA nephropathy. For therapeutic measures, immunosuppressive drugs are utilized but they are not uniformly effective. Moreover, there are not enough supporting studies for IgA nephropathy pathogenesis (Lai et al. 2016; Floege and Feehally 2016). Emerging studies suggest that gut microbiome, intestinal infections and IgA must be focused for a better understanding of IgA nephropathy pathogenesis. This chapter is focused on the role of microorganisms in pathogenesis and therapeutics of IgA vasculitis and IgA nephropathy.

5.2 Role of Microorganisms in the Pathogenesis of IgA Vasculitis

In humans, several pathogenic microbes are considered to induce vasculitis. Among which bacterial infections are predominantly associated with small vessel vasculitis, whereas viruses affect vessels of all the sizes including the aorta (Somer and Finegold 1995).

5.2.1 Bacteria

There are several studies which have shown the involvement of bacteria in the occurrence of vasculitis (Table 5.1). Vasculitis is often regarded as *Staphylococcus aureus* infection resulting due to direct invasion of damaged vessel wall and formation of "mycotic aneurysm" detected in aorta (Lidar et al. 2009).

Table 5.1 List of microorganisms associated with human vasculitis

Bacteria	**Type of vasculitis**	**Reference**
Staphylococcus aureus	Aortitis, GPA, and KD	Lidar et al. (2009)
Streptococcus species	IgA vasculitis, PAN, and KD	Kinumaki et al. (2015), Hashkes (2019), Somer and Finegold (1995), Belizna et al. (2009)
Mycobacterium tuberculosis	TA, IgA vasculitis, cerebral, cutaneous, and retinal vasculitis	Pandhi et al. (2019), Carod Artal (2016), Kim et al. (2006), Shah et al. (1988)
Mycoplasma	IgA vasculitis, cerebral vasculitis, and KD	Soto et al. (2012)
Bartonella henselae	Small vessel vasculitis and endocarditis	Chaudhry et al. (2015)
Salmonella	Aortitis	Pulimamidi et al. (2014)
Burkholderia	GCA	Guillevin (2013)
Clostridium	Aortitis	Sailors et al. (1996)
Viruses	**Type of vasculitis**	**Reference**
Human Immunodeficiency Virus (HIV)	Large-, medium-, and/or small-sized vessel vasculitis, cerebral vasculitis, and CryoVas	Clifford and Hoffman (2015)
Varicella zoster virus (VZV)	Small- and large-vessel vasculitis of the cerebrum, retina, choroid, kidneys, and skin	Haq and Pagnoux (2019), Lidar et al. (2009)
Hepatitis B virus (HBV)	PAN and CryoVas	Lidar et al. (2009)
Hepatitis C virus (HCV)	CryoVas	Ferri et al. (2004), Teng and Chatham (2015)
Cytomegalovirus (CMV)	Vasculitis of GIT, CNS, retina, and cutaneous tissue	Lidar et al. (2009)
Human T acell leukemia virus type 1 (HTLV1)	Necrotizing retinitis and cutaneous vasculitis	Buggage (2003), Haynes et al. (1983)
Epstein-Barr virus (EBV)	Leukocytoclastic vasculitis, granulomatous vasculitis, and large-vessel vasculitis	Pipitone and Salvarani (2008), Kikuta et al. (1993)
Parvovirus B19	IgA vasculitis, PAN, KD, Wegener's granulomatosis, GCA, and CryoVas	Lunardi et al. (2008), Lidar et al. (2009), Lazzerini et al. (2018)
Herpes simplex virus (HSV)	Necrotizing vasculitis of small- and medium-sized lung and peripancreatic arteries	Phinney et al. (1982)
Coronavirus	KD and multisystem inflammatory syndrome in children	Feldstein et al. (2020)
Hantavirus	Cutaneous vasculitis	Pether et al. (1993)
Rubella virus	Cutaneous vasculitis	Larsson et al. (1976)

GIT gastrointestinal tract, *CNS* central nervous system, *TA* takayasu arteritis, *GCA* giant cell arteritis, *PAN* polyarteritis nodosa, *KD* kawasaki disease, *CryoVas* cryoglobulinemic vasculitis

Staphylococcal infection causes neutrophils to produce reactive oxygen species (ROS) and superantigens such as staphylococcal protein A and proteinase 3 to activate autoantigen-specific B and T cells (Cohen Tervaert 2018; Popa and Tervaert 2003). Patients with KD had an increased number of sequencing reads identical to *Streptococcus* species, according to a metagenomic investigation of intestinal microbiota (Kinumaki et al. 2015). Furthermore, the link between *Streptococcus* infection and IgA vasculitis is well-known (Hashkes 2019). Streptococcal antigens such as nephritis-associated plasmin receptor and IgA binding M proteins were detected in kidneys of IgA vasculitis patients. *Streptococcus* species have been implicated in the etiology of vasculitis, including KD and PAN (Somer and Finegold 1995; Belizna et al. 2009). Moreover, *M. tuberculosis* infection has also been linked to Takayasu's arteritis (TA), which is caused by cross-reactivity with vascular peptides (Soto et al. 2012). In immunocompromised patients, *Bartonella henselae*, the main cause of cat scratch disease, has been linked to glomerulonephritis and small vessel vasculitis (Chaudhry et al. 2015). Different types of vasculitis including IgA, cutaneous, cerebral, and retinal vasculitis have been reported to be involved with *M. tuberculosis* infection (Pandhi et al. 2019; Carod Artal 2016; Kim et al. 2006; Shah et al. 1988). *Salmonella* infection was also reported to cause complication within abdominal aorta leading to *Salmonella* aortitis (Pulimamidi et al. 2014). The role of *Burkholderia* infection in vasculitis was first demonstrated by Koening and colleagues, but more research is needed to confirm this finding (Koening et al. 2012). Similarly, *M. pneumoniae* has been linked to IgA vasculitis, CNS vasculopathy, and Kawasaki disease (Teng and Chatham 2015).

5.2.2 Viruses

The diverse group of viruses have been found to be involved in human vasculitis (Table 5.1). Among which cryoglobulinemia (CryoVas), leukocytoclastic, PAN and CNS vasculitis are considered to be associated with HIV infection (Clifford and Hoffman 2015). HIV affects skin and neuromuscular system comparatively more than other organs in patients suffering through PAN. Furthermore, antigens and particles of HIV are found in the vessels of these patients (Cuellar 1998). In vasculitis patients, VZV has been reported to affect the skin, small vessels, kidneys, and CNS (Haq and Pagnoux 2019; Lidar et al. 2009); whereas HBV is primarily associated with two types of vasculitis: PAN and small vessel CryoVas (Haq and Pagnoux 2019). Immune complex-mediated small vessel vasculitis was detected in 10% of HBV patients (Lidar et al. 2009). Initial HBV infection was associated with 10–54% of cases after 6 months (Belizna et al. 2009). Furthermore, HBsAg (Hepatitis B surface antigen) was found in the vessel wall in up to 50% of PAN patients and 30% of systemic vasculitis patients (Maya et al. 2008). Similarly, CryoVas caused by the chronic HCV was found in 50% HCV infected patients out of which 5% patients had HCV-associated CryoVas (Ferri et al. 2004; Teng and Chatham 2015).

Cytomegalovirus (CMV) is considered to cause vasculitis in various organs such as retina, CNS, cutaneous tissue, and GIT (Table 5.1) (Lidar et al. 2009), but whether it can be considered as a causative agent for vasculitis remains unclear as it is less harmful commensal found in 50–55% of healthy vessel (Clifford and Hoffman 2015). Additionally, Human T cell lymphotropic virus type 1 (HTLV-1) infection has also been reported with retinal vasculitis and cutaneous lymphocytic vasculitis (Buggage 2003; Haynes et al. 1983). EBV infection in B cells and various human B cell lymphomas has also been associated with KD and lead to granulomatous vasculitis pathogenesis (Pipitone and Salvarani 2008; Kikuta et al. 1993). Furthermore, parvovirus B19 has been linked to a number of other kinds of vasculitis, including PAN, KD, GCA, Henoch-Schonlein purpura, and CryoVas (Lunardi et al. 2008; Lidar et al. 2009; Lazzerini et al. 2018). Acute hantavirus contributes to the pathogenesis of cutaneous vasculitis, whereas parvovirus B19 linked vasculitis is thought to be caused by direct damage to the diseased vessel wall (Pether et al. 1993). Moreover, necrotizing vasculitis was found in small- and medium-sized lung and peripancreatic arteries in neonates with HSV infection (Phinney et al. 1982). A child with congenital rubella syndrome also developed cutaneous vasculitis (Larsson et al. 1976).

CMV, HIV, HBV, and parvovirus B19 are only a few of the viruses that have been linked to vasculitis through various methods. Invasion of malignant $CD4^+$ cells infected with HTLV-1 has also been reported to have a role in the etiology of vasculitis (Table 5.1). However, only a few viruses have been detected in vasculitis using various techniques such as ELISA, PCR, and immunohistochemistry (IHC), indicating that there are still unidentified pathogenic viruses in vasculitis, particularly IgA vasculitis (Kiselev et al. 2020).

5.2.2.1 SARS-CoV-2

The link between new coronavirus and KD has been known since the 1970s (Esper et al. 2005; Shirato et al. 2014). However, before the latest COVID-19 pandemic epidemic, this research received a very little attention. Physicians noted symptoms in children that were comparable to those of KD, toxic shock syndrome (TSS), and multisystem inflammatory syndrome in the early stages of the COVID-19 outbreak (Jiang et al. 2020). When PCR cycle thresholds for SARS-CoV-2 were compared between severe COVID-19 and COVID-19 children with multisystem inflammatory syndrome, the PCR thresholds for SARS-CoV-2 in children with multisystem inflammatory syndrome were higher (Henderson and Yeung 2021). Moreover, multisystem inflammatory syndrome patients exhibited antibody response against SARS-CoV-2 and presented specific autoantibodies for immune cell, gastrointestinal and endothelial antigens (Gruber et al. 2020).

Furthermore, the emerging studies suggest the crucial role of SARS-CoV-2 in IgA vasculitis pathogenesis. Few reports have documented IgA vasculitis cases post-COVID-19. A recent study has reported that a healthy 94 years old man who had no previous vasculitis history developed leukocytoclastic vasculitis post COVID-19 vaccination (Grossman et al. 2022). The study suggests that both IgA vasculitis and Henoch-Schönlein purpura may be post-infectious (Grossman et al. 2022). A

30 years old man who had no IgA vasculitis history, developed the COVID-19 symptoms and new onset of abdominal pain, painful purpuric rash and arthralgia. SARS-CoV-2 infection along with dysmorphic hematuria and nephrotic range proteinuria also demonstrated leukocytoclastic vasculitis (Li et al. 2021). Similarly, a case report of 26-year-old female with COVID-19 infection showed COVID-19 associated CNS vasculitis which was further confirmed through biopsy (Timmons et al. 2021). An unusual example of cutaneous small vessel vasculitis with koebnerization was reported in a case study on a 30-year-old individual who tested positive for COVID-19 (Fatima et al. 2021). According to one study, COVID-19 may be linked to cutaneous symptoms even after recovery (Fatima et al. 2021). Though it is possible that the IgA vasculitis in these patients is unrelated to the presence of COVID-19, the presence of symptoms in conjunction with a positive COVID-19 PCR indicates, SARS-CoV-2 as IgA vasculitis trigger. Nonetheless, anti-SARS-CoV-2 IgA was the first antibody found in COVID-19 after 2 days of onset, but IgM and IgG seroconversion takes about 5 days (Yu et al. 2020). Based on the identification of anti-SARS-COV-2 IgA and negative IgG in some patients, a clear link between chillblain-like lesions with probable vascular injury and COVID-19 has been proposed (El Hachem et al. 2020). Similarly, several case reports and observations in the literature imply that COVID-19 disease has a role in causing IgA vasculitis (Suso et al. 2020; Nishimura et al. 2022; Mayron et al. 2021; Obeid et al. 2021). It has been found that endothelial inflammation, dysfunction and apoptosis occur in COVID-19 patients (Becker 2020). Moreover, endothelial cells are triggered during conditions such as infection, hypoxia, oxidative stress, and environmental toxins. Furthermore, the widespread expression of Angiotensin converting enzyme 2 (ACE2) receptors in endothelial cells elevates the possibility of infection and vascular damage from SARS-CoV-2 binding (Becker 2020). Within the endothelium, inflammatory cells and viral inclusions accumulate. In a study, the tissue specimens were autopsied, and lymphocytic endotheliitis was discovered (Varga et al. 2020). Thus, it is possible that endotheliitis and endothelial cell damage in COVID-19 patients can lead to vasculitis. Still, studies with higher sample sizes are needed in future to confirm the relevance of SARS-CoV-2 infection in IgA vasculitis.

5.3 Role of Gut Microbiota in IgA Vasculitis

The role of gut microbiota in vascular diseases has not been well studied. Alteration within bacterial signatures was observed in inflammatory vasculitis syndrome (Forbes et al. 2016). Previous study on inflammatory vasculitis syndrome animal model, and mouse gamma herpes viral infection (MHV68) showed increase in MHV68 infection and inflammatory vasculitis syndrome with earlier mortality, after antibiotic depletion of gut bacteria (Tariq and Clifford 2021). Broad-spectrum oral antibiotics shortened the survival in MHV68 infected mice from 60 to 20 days (Tariq and Clifford 2021). Overall, the study suggested a central role of the endogenous microbiota in not only preventing MHV68 infection but also in inflammatory vasculitis syndrome progression.

Furthermore, a study of children with IgA vasculitis found that their gut microbiota was higher than that of normal children. Bacteroidetes, Proteobacteria, Actinobacteria, and Firmicutes are the most common bacteria found in children's intestinal flora. Proteobacteria and Actinobacteria, for example, have been linked to organ involvement in IgA vasculitis (Forbes et al. 2016). The development of allergy disorders has been linked to changes in the gut microbiota. The microbial diversity and composition in the feces of 85 children with Henoch-Schonlein Purpura and 70 healthy children were compared in a study (Wang et al. 2018). The findings revealed considerable alterations in the gut microbiota's composition and structure (Wang et al. 2018). However, more animal and human studies are needed to back up the findings of the previous investigations.

5.4 Role of Microorganisms in IgA Nephropathy

Mucosal infections have been linked to malfunctions in the regulation of local IgA responses, which could lead to IgA nephropathy (Gesualdo et al. 2021). Currently, three ideas have been considered to demonstrate the potential relevance of mucosal infections in IgA nephropathy pathogenesis via a variety of pathogens and changes in the gut microbiota (Rollino et al. 2016).

The first hypothesis proposes that particular infections are involved in the initiation and progression of IgA nephropathy. Some pathogens, such as *Staphylococcus aureus*, HSV, HCV, and EBV, have been detected in the renal tissues of patients with IgA nephropathy (Park et al. 1994; Tomino et al. 1987; Suzuki et al. 1994; Sharmin et al. 2004; Iwama et al. 1998). These pathogens can interact with the binding sites in the glomerulus, causing the kidney damage. In the case of *Helicobacter pylori* infection, elevated levels of hypogalactosylated-IgA1 (Gd-IgA1) were detected in IgA nephropathy patients (Liu et al. 2020; Satoh-Takayama et al. 2020). Furthermore, an investigation using a mouse model of the poliovirus vaccine reveals that greater serum levels of IgA are present in kidney histopathology (Soylu et al. 2008). Similar to the renal pathological aspects of IgA nephropathy, a study on respiratory syncytial virus, the Sendai virus, demonstrated ability to enhance the production of inflammatory cytokines such as IL-6 to cause mesangial proliferation (Kobayashi et al. 2003; Hu et al. 2019). However, this concept does not have widespread backing among scholars. Several alternative viewpoints have been expressed, implying that the pathogens mentioned above play a role in patients with different glomerular diseases such as CMV in membranous nephropathy, *Haemophilus parainfluenzae* in non-IgA glomerulonephritis, and SLE (Park et al. 1994; Suzuki et al. 1994). Few researchers deny that these findings were only observed in a few situations (He et al. 2020). Moreover, different methods for detection of pathogens and collection of biopsy tissues may also contribute to these inconsistencies. For example, impurities within DNA (e.g., polymerase-inhibiting substances), while performing PCR result into the non-specific binding and affect the results.

According to the second hypothesis, chronic and prolonged exposure causes mucosal infections, which are linked to IgA nephropathy. Tonsillectomy, for example, has been shown in studies to help IgA nephropathy patients by lowering hematuria and proteinuria while also improving renal function (Miura et al. 2009; Muto et al. 2017). Tonsillectomy with immunosuppressants has also been proven to elicit clinical remission in early-stage IgA nephropathy patients and may also aid in long-term renal survival prevention (Kawamura et al. 2014; Komatsu et al. 2008; Xie et al. 2003). However, the beneficial results of tonsillectomy have not been constant across the trials, suggesting that disease heterogeneity exists among different ethnic groups or races (Rasche et al. 1999; Piccoli et al. 2010).

The third hypothesis suggests that dysbiosis among the gut microbiota can impact both systemic and local immune responses. By regulating immune responses to microorganisms, the gut microbiome keeps the host in normal condition. When the host's innate and adaptive immune systems build biochemical barrier between the gut microbiome and host, dysbiosis occurs and it leads to severe inflammatory response. In autoimmune and chronic inflammatory illnesses, abnormal immune responses have resulted in increased infiltration of pro-inflammatory cells such as DCs, neutrophils, and Th1 and Th17 cells (Brown et al. 2019). These changes in the gut microbiome may increase antigen burden, and induce B cell class switching leading to excessive IgA synthesis (Kiryluk and Novak 2014; Rollino et al. 2016).

Furthermore, long-term antigenic exposure may cause changes in the intestinal permeability, inflammation, and MALT activation (Coppo 2015). For instance, the ectopic colonization of *Klebsiella* sp. has been linked to the immune system's constant activity. The outer membrane protein of *Klebsiella pneumoniae* 2H7 is thought to act as a potent Th1 cell inducer, leading to Th1 cells' accumulation in mice (Atarashi et al. 2017; Chen et al. 2014). Similarly, *Candida albicans* colonization has been demonstrated to stimulate IL-17/IFN-γ release by Th17 cells (Zielinski et al. 2012; Mayer et al. 2013). Thus, gut microbial colonization has been shown to impact intestinal immune status by several studies. Moreover, IgA nephropathy experimental mice model in a GF environment or employing broad-spectrum antibiotics eliminated the intestinal infections that could lower IgA1 serum levels (McCarthy et al. 2011; Chemouny et al. 2018).

5.5 Therapeutic Aspects of Gut Microbiota in IgA Nephropathy

Presently, there is no therapeutics available for IgA nephropathy with respect to gut microbiota, which may be due to its unexplained pathogenesis. Hypothesis suggests that the changes within gut microbiome and undue IgA immunity in IgA nephropathy can result in excessive IgA production in genetically susceptible individuals. Therefore, gut microbiota modulation and excessive mucosal immunity suppression may result into a promising therapeutic strategy in the future.

5.5.1 Modulation of Gut Microbiota

The pathogenesis of IgA nephropathy demonstrates that control of the gut microbiota entails: (1) pathogen elimination, (2) microbial diversity restoration, and (3) metabolite regulation to normalize IgA levels. Pro-inflammatory immune responses have been linked to the gut microbiome. Several possible IgA nephropathy therapies for the gut microbiome including fecal microbiota transplantation (FMT), are now being investigated.

When broad-spectrum antibiotics were given to humanized 1KI-CD89Tg mice, the levels of hIgA1-mIgG in the circulatory system were decreased (Chemouny et al. 2018). Additionally, the study revealed a decrease in proteinuria (Chemouny et al. 2018). Furthermore, new techniques are currently being developed, in which researchers have created programmed inhibitor cells that stimulate antibacterial activity of type VI secretion system against certain bacteria species or strains. The usual microbial community is unaffected by this approach, and resistance is rare (Ting et al. 2020). Several autoimmune diseases, metabolic abnormalities, and intestinal infections are caused by abnormal changes in microbial metabolites and modification of the host's innate immune response (Singh et al. 2014; Wahlstrom et al. 2016; Jacobson et al. 2018). Short chain fatty acids (SCFAs), such as acetate, butyrate, and propionate have long been regarded as critical metabolites. The acetate has been demonstrated to reduce the amount of IgA^+ B cells and $CD8^+$ T cells in NOD mice's Peyer's patches while increasing the percentage of Tregs (Huang et al. 2020). Moreover, butyrate was found to diminish inflammation in a mouse model by stimulating colonic epithelium to produce IL-18 by activating the G protein-coupled receptor 109a (GPCR109a) (Singh et al. 2014). Thus, SCFAs appear to lower the IgA synthesis and improve hyperactive immunological responses.

Aside from antibiotics and SCFAs, many other innovative methods for addressing the immunological problems are being used, such as FMT, which prevents disease by restoring a diverse microbial community (Frisbee and Petri Jr 2020). FMT may reduce the IgA synthesis by increasing SCFAs concentrations (Paramsothy et al. 2019). Patients with IgA nephropathy are being studied through clinical studies to see if, FMT is safe and effective (NCT03633864). Several studies have explored the use of probiotics or prebiotics as a strategy to alter the gut microbiota and host immune responses over the last few decades (Sanders et al. 2019). Few probiotic species that produce acetic and lactic acids, such as *Lactobacillus* and *Bifidobacterium* have been utilized to lower luminal pH, thereby decreasing the IgA production in mice (Huang et al. 2020; Flint et al. 2015).

Apart from utilization of antibiotics and SCFAs, various other new approaches for immune conditions have been used for immune conditions such as FMT, which prevents disease state by restoring a diverse microbial community (Frisbee and Petri Jr 2020). Increasing the concentrations of SCFAs by FMT may decrease the production of IgA (Paramsothy et al. 2019). Clinical trials are conducted on patients with IgA nephropathy for evaluating safety and efficacy of FMT (NCT03633864). Since, past decades there is an increase in research on probiotics or prebiotics as a way to modulate the gut microbiota and host immune responses (Sanders et al.

2019). Few probiotic microorganisms that produce acetic and lactic acids, such as *Lactobacillus* and *Bifidobacterium*, have been utilized to lower luminal pH and hence inhibit IgA synthesis in mice (Huang et al. 2020; Flint et al. 2015).

5.5.2 Suppression of Excessive Mucosal Immune Responses

Overproduction of Gd-Ig1 antibodies is linked to gastrointestinal immune diseases. Excessive mucosal immune responses can be suppressed, which could lead to a potential treatment approach. Use of systemic immunosuppressants like budesonide can cause severe infections such as hyperglycemia or intestinal perforation. As a result, the role of corticosteroids in IgA nephropathy is unknown. Advanced stage patients of IgA nephropathy were treated with prednisone in combination with cyclophosphamide or mycophenolate mofetil in combination with corticosteroid (NCT03218852; NCT02981212). NEFECON was reported to show a decrease in proteinuria levels in a phase 2b trial and reported to be safe and well tolerated (Fellström et al. 2017). Nevertheless, with NEFECON no pharmacokinetic data have been reported in IgA nephropathy patients. Because studies showed that a portion of NEFECON is absorbed, there is concern about its systemic effect in IgA nephropathy patients. Moreover, because NEFECON has the ability to directly influence mucosal immune responses, further detailed research is needed. A phase 3 study on NEFECON oral administration in primary IgA nephropathy patients is currently underway to assess its efficacy, safety, and tolerability in these patients (NCT03643965).

5.6 Conclusions

Infectious entities must be considered as potential causal factors in IgA vasculitis and IgA nephropathy. Evidences from the gut microbiome suggest for the relevance of abnormal mucosal immune responses in the development of IgA nephropathy. Numerous microbes including bacteria and viruses have been linked to human vasculitis, as detailed in several investigations. Despite the ongoing research on IgA vasculitis, the majority of investigations were unsuccessful to identify the causal pathogens, and the link between IgA vasculitis and infection remains unknown. Since undiscovered viruses that can induce IgA vasculitis may exist, further research is necessary to identify these viruses. Moreover, to validate the presence of previously unknown microorganisms in human IgA vasculitis and to develop novel therapeutic options for pathogen-associated vasculitis, more animal models, and clinical trials are needed.

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6 Microorganisms in Pathogenesis and Management of Immune-Mediated Glomerulopathies

K. Thangavel and A. Sankaranarayanan

Abstract

Pathogenesis in autoimmune diseases entails a smash of immune forbearance, although many mechanisms may contribute to the development of such phenomenon. In many autoimmune diseases, it is extensively recognized that a set of conditions resulting from tissue inflammation and amalgamation of intrinsic and environmental factors including pathogens persuade the development of autoimmunity. Most of the infections lead to glomerulopthies due to *Streptococcus* (27.7%) and *Staphylococcus* (24.4%) and other pathogens have been involved. Glomerulopthies and other glomerular diseases usually result from various mechanisms including glomerular deposition of immune complexes containing bacterial antigens. Immune complex mediated glamarulopathy is one of the most serious manifestations of lupus disease. Severe inflammation and necrosis and regardless of therapy, often leads to renal failure, are important characteristic features of this disease. The classic histopathological lesion is thickening of glamarular basement membrane owing to the deposition of immune complex. The management strategies include culture and treatment of any remaining streptococcal related infections. Protective antibiotic treatment is justified in populations at risk during epidemics and in siblings of index cases. However, recognizing patients who will benefit from treatment continues to be a clinical challenge.

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Keywords

Autoimmunity · Immune-mediated glomerulopathy · Necrosis · Renal failure · Pathogen diagnosis · Antibiotic therapy

6.1 Introduction

Immune complex mediated glomerulopathies are a set of conditions resulting from inflammation and glamarular membranous tissue where abnormal immune complexes are formed or deposited (Noris et al. 2019). Pathogenesis in autoimmune diseases entails a break of immune forbearance, although many mechanisms may contribute to the development of such a phenomenon. In many autoimmune diseases, it is widely established that some amalgamation of intrinsic and environmental factors including pathogens persuade the development of autoimmunity. Factors influencing the site of deposits and glamarular membrane injury model include immunoglobulin type their specialied potential to activate complement and cellular immunity (Jha et al. 2013).

The primary or systemic kidney diseases mediated through the immune system dysregulation in Glamarular membrane. Moreover, the glomerulus represents the anatomical entity commonly involved, generally as the expression of inflammatory cell invasion or circulant or in situ immune complex deposition (Jha et al. 2013; Noris et al. 2019). This chapter summarizes the involvement of microorganisms and gut microbiota in pathogensis of immune-mediated glomerulopathies and its management.

6.2 Glomerulopathies

The blood filtering function of kidney is distressed by damaging the glomeruli through various chronic and acute diseases conditions. Glomerular diseases comprise many conditions led by intrinsic and environmental origin, but they drop into two major categories (Nagata 2009), i.e. Glomerulonephritis and Glomerulosclerosis. Former one describes the swelling of membrane tissue and where the later affected the scarring or hardening of the tiny blood vessels of the kidney (Nagata 2009). However both have different causes, at the end they can lead to kidney failure. Glomerulopathy is a group of diseases distressing the glomeruli of the nephron. Such diseases can include inflammatory or non-inflammatory pattern of succession. Because the term glomerulitis exists for inflammatory conditions, glomerulopathy sometimes carries a non-inflammatory implication (Nagata 2009; Wetmore et al. 2016).

Furthermore, glomerulopathy and glomerulonephritis are being recognized as closed associated climinal and pathological conditions (Noris and Remuzzi 2015). Glomerulopathy includes different stages of glamarular tissue injury, inflammation, and associated infection elsewhere in the body, such as strep throat or scarlet fever,

upper respiratory infection or tonsillitis (Noris and Remuzzi 2015). The differential diagnosis of proliferative glomerulonephritis includes infections, autoimmune disorders, and paraproteinemias due to monoclonal gammopathies (Alchi and Jayne 2010).

Glomerulopathies infection may be by direct or drug mediated toxicity to kidneys or an infection through out the body like diabetes or lupus (Alchi and Jayne 2010). The causes and categories may overlap: for example, diabetic nephropathy is a form of glomerular disease that can be placed in two categories: systemic diseases, since diabetes itself is a systemic disease, and sclerotic diseases, because the specific damage to the kidneys is associated with scarring (Alchi and Jayne 2010; Noris and Remuzzi 2015; Noris et al. 2019; Sekuli et al. 2021).

6.2.1 Glomerulopathies Associated with Bacterial Infections

In majority of the patients, glomerulopathies caused by *Streptococcus* and *Staphylococcus infections*, but other pathogens have also been reported (Table 6.1). Glomerulopathies occasionally develops rapidly after an infection in other parts of the body. Acute post-streptococcal glomerulonephritis (PSGN) can arise after strep throat or, in unusual cases, due to a skin infection such as impetigo (Jasmin et al.

Table 6.1 List of various microorganisms involved in pathogenesis of Glomerulopathies (Jasmin et al. 2021; Mosterd et al. 2021)

Bacterial pathogens	Viral pathogens	Helminths	Protozoans
Staphyloccoccus aureus	Influenza virus	*Schistosoma mansoni*	*Leishmania donovani*
Staphyloccoccus epidermidis	Epstein–Barr virus	*Schistosoma japonicum*	*Plasmodium malariae*
Staphyloccoccus albus	Hepatitis B and C	*Schistosoma haematobium*	*Plasmodium falciparum*
Streptococcus pneumoniae	Human Immunodeficiency virus	*Wuchereria bancrofti*	*Toxoplasma gondii*
Streptococcus virdans	Cytomegalovirus	*Brugia malayi*	*Trypanosoma cruzi*
Streptococcus pyogenes	Varicella zoster	*Onchocerca volvulus*	
Salmonella typhi	Mumps		
Salmonella paratyphi	Rubella		
Salmonella typhimurium			
Mycobacterium leprae			
Mycobacterium tuberculosis			
Neisseria meningitidis			
Treponema pallidum			

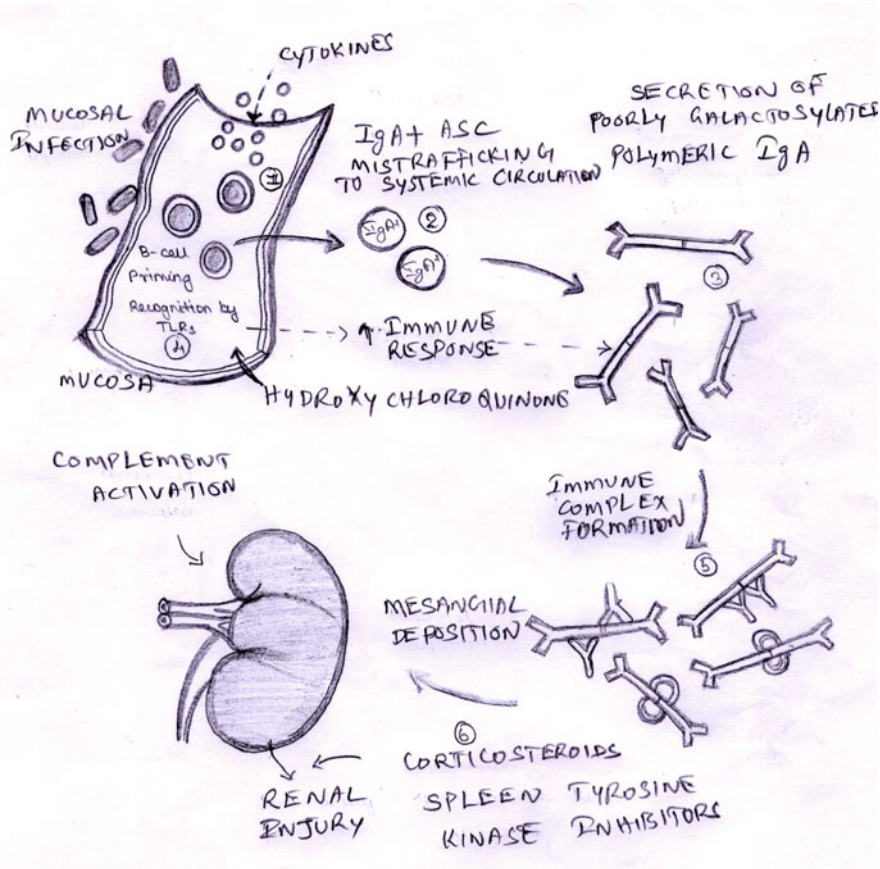

Fig. 6.1 Different stages of immune complex mediated glamaruopathies

2021). The *Streptococcus* bacteria do not attack the kidney directly, but the overproduce antibodies due to its infection, antibodies circulated in the blood, deposited in the glomeruli and causing damage (Fig. 6.1). PSGN leads to swelling, concentrated discharge of urine and hematuria. PSGN affect children between the ages of 3 and 7, although at any age and especially male (Jasmin et al. 2021) and for short time. Conversely, few cases need dialysis or transplantation to reinstate renal function due to permanent kidney. Bacterial endocarditis so frequently leads to chronic kidney disease (CKD) (Mosterd et al. 2021) in few cases.

Acute typhoid during *Salmonella typhi* infection is followed by fever, splenomegaly, and gastrointestinal symptoms. Brutal cases leads to shock and acute renal failure as a part of dispersed intravascular coagulation but the said one are rare (Mosterd et al. 2021). Over mesangial proliferative glomerulopathies happen in 2% of the cases, but 25% of the cases microscopic hematuria and mild proteinuria may occur. The patients with schistosomiasis and coexisting *Salmonella* infection of the

urinary tract may be the ancillary problems in glomerulopathies (Mosterd et al. 2021).

6.2.2 Glomerulopathies Associated with Viral Infections

Hepatitis virus, parvovirus B19, measles, and Epstein–Barr virus infections can cause acute and chronic glomerulopathies. HBV, HCV, and HIV cause the most frequent infections (Mosterd et al. 2021). The pathogenic mechanisms comprise deposition or in situ formation of exogenous immune complexes; autoantibody formation directed to endogenous antigen modified by viral injury; virus-induced release of proinflammatory cytokines, chemokines, adhesion molecules, and growth factors; and direct cytopathic effects of viral proteins (Mosterd et al. 2021).

In HIV infected cases, 5–10% of people have kidney failure, prior to development of AIDS. Acute nephropathy begins with heavy proteinuria and progresses to toal kidney failure propably within a year (Jasmin et al. 2021) in HIV cases. Attempts are underway for therapies that can slow down or overturn this quick deterioration of renal function, but some promising solutions involving immunosuppression are perilous because of the patients' previously compromised immune system diseases (Jasmin et al. 2021; Mosterd et al. 2021).

6.2.2.1 COVID-19 and Immune-Mediated Glomerulopathies

During the COVID-19 pandemic, several patients have undergone additional diagnosis for the possible causes and association with glomerulopathies. Disease conditions such as glomerular abrasions were reported in a minority of patients with COVID-19, with additional symptoms associated with collapsing focal segmental glomerulosclerosis (FSGS). These complex type symptoms were referred to as COVID-associated nephropathy (COVAN) (Huang et al. 2020). In case of such patients, more prevalent symptoms were found to be related with nephritic range proteinuria and acute kidney injury (AKI). Clinical diagnosis and pathological characterizations of the patients with this complex COVAN were found to be almost similar to HIV-associated nephropathy (Huang et al. 2020). Further, this COVAN occurred comparatively higher proportion in Black individuals and the persons with Apolipoprotein L (APOL1) genotypes were found to be high risk category. Other forms of glomerular distress such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane antibody disease and IgA nephropathy have also been moderately associated with COVID-19 (Huang et al. 2020).

In rare cases, relapse of pre-existing glomerular disease have been reported shortly after administration of COVID-19 vaccines such as mRNA-1273 and BNT162b2 (Prendecki et al. 2020). However, these are overall rare and a causal link with the COVID-19 vaccine is not firmly established (Uppal et al. 2020). Conversely, there are no exact studies to guide pandemic-related modifications to the treatment of glomerular disease. Hence, it is recognized from the reports in recent

past that SARS-CoV-2 inexplicably affects patients with different forms of kidney disease including glomerulopathies.

6.3 Immune-Mediated Nephropathies

Immune complex mediated nephropathy is one among the severe implications of lupus disease. It is observed that brutal inflammation and necrosis, and regardless of therapy, progresses to renal failure (Jefferson 2018). Development of complement system is being the vital protective mechanism provided through innate immunity against several infections, underlying towards the clearance of immune complex deposits and cellular debris and assisting the adaptive immune response (Ricklin et al. 2010; Jefferson 2018).

The immune complex system efficiently destroys microorganisms, concomitantly, a strict regulation guarantee that complement does not harm host cells and tissues. In the proper function of body's immune system, it generates as well activate antibodies and immunoglobulins to protect the body against pathogens (Ricklin et al. 2010). In case of any disparity in précised coordination between complement activation and inhibition can lead to various diseases. In an autoimmune disease, the immune system creates autoantibodies, that attack the body (Ricklin et al. 2010). Autoimmune diseases may be systemic in progression, or they may affect only specific organs or regions. Faulty gene expression in complement system may develop a complement deficiency or leads to an altered function (Jefferson 2018). The auto antibodies which developed acquired complement abnormalities are reasons for various diseases, including kidney diseases, i.e. C3 glomerulopathy, membranoproliferative glomerulonephritis (MPGN), and atypical hemolytic uremic syndrome (aHUS) (Ricklin et al. 2010; Józsi et al. 2014; Jefferson 2018).

Several elements of immune system are involved in glomerular injury resulting in many clinical and pathologic results (Fig. 6.1). Small deformities of hematuria and proteinuria might be the sign of profound proteinuric states such as nephritic syndrome or glomerular inflammation that at times leads to a rapidly declining course (Couser 1999; Uta Erdbruegger et al. 2004).

Glomerulopathies may be induced by exogenous compounds which lead to toxicity, and caused by inducing an immune or autoimmune response. Glomerular tubules are more frequently the target of toxicity as they absorb and concentrate components of filtrate (Couser 1999). Damage to endothelial cells may account for thrombotic microangiopathy in response to calcineurin inhibitors. Endothelial cells are also likely to be the target in drug-induced small vessel vasculitis (Couser 1999).

6.4 Glomerulonephritis Caused by Immune Complex Deposits

Membranous nephropathy (MN) characterized with a non-inflammatory, organ-specific autoimmune disease distressing the glomerulus which progresses the immune deposits on the outer portion of Glamarular Basement Membrane.

Membranous nephropathy may be caused by exposure to gold, mercury, and some other drugs; this is antibody mediated and presumably the targets are altered podocyte surface molecules (Sethi and Fervenza 2011). Inhibitors of the mammalian target of rapamycin (mTOR) cause proteinuria, possibly through effects on vascular endothelial growth factor, inhibitors of which are involved not only in proteinuria, but also in thrombotic microangiopathy (Sethi and Fervenza 2011).

Membranous nephropathy can arise in all age groups, from childhood to old age. In the adult population, it is the widespread cause of Nephrotic Syndrome (NS), as per the report, it was observed that it affects children (3%) under 13 years of age and adolescents (18%) (Foster and Ord 2019). Occurrence of 1.5% glamarulapathies in children with Nephrotic Syndrome has been validated through International Study of Kidney Diseases in Children (ISKDC). In major group of children, it is secondary to infections, chiefly hepatitis B in endemic areas and systemic diseases, mainly SLE. In the remaining cases, it is defined as "idiopathic." Malignancy associated membranous nephropathy unusual in the pediatric population (Nakanishi et al. 2013).

6.5 Glomerulopathies and Gut Microflora

The intestinal epithelial wall acts as a platform in which the colonization of gut microbiome, considered as the main source to health and disease. Dysregulation in the interactions between the gut microbial ecosystem and the neighboring mucosal immune system have been identified in autoimmune diseases and glomerulopathies (Jasmin et al. 2021). Research reports are revealed that the association between the gut dysbiosis and other immune-mediated diseases, including systemic lupus erythematous (SLE), ankylosing spondylitis, and rheumatoid arthritis (RA), where abnormal immune response affects sites distant from the gut. Further the association between the gut microbiota and extra-intestinal immune-mediated diseases not clear (Jasmin et al. 2021). The deposition of IgA1 (particularly, galactose-deficient IgA1) in the glomerular mesangium is mediated through IgA nephropathy (IgAN), a primary source of glomerulonephritis (Jasmin et al. 2021).

6.6 Management of Glomerulopathies

Glomerulopathies are being one of the major health care threats and demonstrated as he main source of chronic kidney disease (CKD). However, many treatment protocols for glomerulopathies focused towards the kidney damage management. Tremendously less and nonspecific information regarding the treatment of CKD specifically caused by glomerulopathies is available. Apparent risk factors for succession of different forms of glomerulopathies to CKD include the presence of proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis (Moeller and Chia-Gil 2020). Holistic and conformist treatment of all chronic renal diseases includes blood pressure management with Renin-angiotensin aldosterone system (RAAS) inhibitors, ruling out edema with diuretics and a low sodium diet, avoidance of

nephrotoxins and temperance of dietary protein intake. Other treatments, such as control of dyslipidemia, could reduce the cardiovascular risk so common in CKD patients (Moeller and Chia-Gil 2020).

Moreover, renal biopsy is not frequently chosen in PSGN but may be essential to confirm the diagnosis when it presents with unusual clinical features, such as nephrotic proteinuria, decreased C3 levels and swelling renal dysfunction. For the prevention of PSGN, early antibiotic treatment is advisable. Treatment with penicillin or oral phenoxymethyl or phenoxyethyl penicillin G 250 is required for the period of 7–10 days. In persons allergic to penicillin, erythromycin has been suggested. Cephalosporins can also be used with equal or even improved results (Moeller and Chia-Gil 2020).

In addition, the management of acute nephritic syndrome includes restriction of fluid and sodium intake and the use of loop diuretics to treat circulatory congestion. An oral long acting calcium antagonist is generally satisfactory to bring down the hypertension normal. Nitroprusside is optional in rare cases with hypertensive encephalopathy. Hemodialysis or peritoneal dialysis is obligatory in 25% to 30% of adults but rarely in children (Moeller and Chia-Gil 2020).

6.7 Conclusions

Antigens emerged against bacterial infections are implicated in the onset and progression of different forms of glomerulopathies. Substantial evidence is availale and entail that *Staphylococcus aureus* exerts a direct pathogenic role in glomerulopathies. Other bacterial pathogens may not be directly related to the development of glomerulopathies. However, the pathogenic invasion and deposition of immune complexes secondary to infections may contribute to glamaruopathies and othehr forms of renal damage. However, there are several limitations when assessing data about the role of specific pathogenic microbes in glomerulopathies. Most interesting findings like hLAMP-2 in pauci-immune crescentic glomerulonephritis or the role of *Haemophilus parainfluenzae* in IgA nephropathy rely on robust data. The lack of proof of causality is also a problem with studies in which an abundance of bacterial strains was detected in patients with different forms of glomerulopthies. Hence, a prisiced and comprehensive finding and characterization of glomerulopathies in more convincing pathomechanistic experimental models is suggested as the vital need towards resolving these complications.

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Microorganisms in Pathogenesis and Management of Autoimmune Addison's Disease (AAD)

7

Firdosh Shah and Mitesh Kumar Dwivedi

Abstract

Autoimmune Addison's disease (AAD) is an organ specific autoimmune disease which causes primary adrenocortical insufficiency. In AAD, autoantibodies and autoreactive T cells target cytochrome P450 21-hydroxylase enzyme, which is a major self-antigen. Similar to other autoimmune diseases, both genetic and environmental factors play an important role in AAD. Many researchers have proposed common pathways that link immunity and bacterial and viral infections in AAD. Moreover, studies have shown the association of viral infections with the initiation of AAD progression. The chapter summarizes the current aspects of microorganisms' involvement in the pathogenesis and management of AAD.

Keywords

Autoimmune Addison's disease (AAD) · Autoimmunity · Adrenal gland · Adrenocortical insufficiency · Cytochrome P450 21-hydroxylase enzyme · Human immunodeficiency virus (HIV) · Cytomegalovirus (CMV)

7.1 Introduction

Autoimmune Addison's disease (AAD) is a rare autoimmune disease that occurs due to complex interaction of genetic, environmental and immunological factors and results in symptomatic adrenocorticol insufficiency and dependency on corticosteroid replacement therapy throughout life (Betterle et al. 2002). Dr. Thomas Addison from Guy's Hospital, London reported the AAD's first case in late mid-nineteenth

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century and described adrenocortical insufficiency and changes in adrenal glands as major symptoms (Addison 2009). The patients exhibited tumors or tuberculosis of adrenal glands, except the one case of idiopathic adrenal atrophy, now known as autoimmune Addison's disease (AAD).

In most countries, the possible etiology behind primary adrenal insufficiency is represented as autoimmune adrenalitis (Neufeld et al. 1981; Ten et al. 2001). Malignancy and hemorrhage are considered as less frequently encountered cause of AAD, whereas if specifically considering cases in males, mostly rare X-linked condition and adrenoleukodystrophy are reported as a reason behind occurrence of AAD (Neufeld et al. 1981; Ten et al. 2001). In the past decades, tuberculous infiltration of the adrenal glands was considered as major cause of primary adrenal insufficiency globally and still is one of the persistent causes in several developing countries (Addison 2009; Soule 1999). Primary adrenal insufficiency is rare with an annual incidence of 4.7–6.2 per million in white populations with a prevalence of 93–140 per million (Laureti et al. 1999; Kong and Jeffcoate 1994; Mason et al. 1968). It is prevalent in women, irrespective of age; however, it is mostly reported between the 30 and 50 years of age groups (Kong and Jeffcoate 1994). In order to restore good health, AAD patients have to rely on supplementation therapy throughout their life, as the steroid hormone releasing cells of the adrenal cortex are attacked by immune cells which results into organ failure and lack of steroid hormone synthesis within adrenal gland of AAD patients (Bornstein 2009; Bratland and Husebye 2011). These patients suffer through higher rate of morbidity, mortality and reduced quality of life (Lovas et al. 2002; Erichsen et al. 2009; Bensing et al. 2008, 2016). Therefore, there is a need of improving insights regarding the unrevealed pathological mechanisms associated with AAD in order to form the grounds for rational design of molecular and cellular strategies which could be targeted for the treatment of the disease. Similar to most of the autoimmune diseases, AAD is also considered as a multi-factorial disease which involves several factors such as genetic, environmental, and failure to control autoreactive lymphocytes at different stages (Goodnow 2007). Various genetic risk factors are known to contribute to AAD, especially major histocompatibility complex (MHC) but hardly something is known about environmental factors (Erichsen et al. 2009; Skinningsrud et al. 2011). Suspected environmental factors which causes autoimmune diseases include infectious agents such as bacteria, viruses, and other pathogens (Ercolini and Miller 2009). Unlike other autoimmune diseases, no specific infectious agents have been identified for AAD (Christen and Hintermann 2018; Lassmann et al. 2011; Hyoty 2016). However, several pathogens are considered to infect the adrenal cortex and may also contribute to adrenal insufficiency (Paolo and Nosanchuk 2006). In this chapter, we highlight the role of infectious agents in the disease development and role of gut microbiota and probiotics in the management of AAD.

7.2 Role of Microorganisms in the Pathogenesis of Autoimmune Addison's Disease

A variety of microorganisms have been reported to infect adrenal gland, adrenal cortex and cause adrenal insufficiency (Paolo and Nosanchuk 2006). These infectious agents cause opportunistic infections, primarily affecting immunocompromised individuals. The infectious agents involved in the AAD mainly include bacteria, viruses, fungi, and parasites. Among this infectious agents, bacteria and viruses are considered of major relevance with AAD just like any other autoimmune endocrinopathies. In fact other microbes like *Paracoccidioides brasiliensis* or *M. tuberculosis* with a tropism for the adrenals are not endemic in the Western world (Glaziou et al. 2014; Bocca et al. 2013). In the below sub-sections, we summarize the involvement of bacteria and viruses in pathogenesis of AAD.

7.2.1 Bacteria

Bacterial infection influences the release of endotoxins or exotoxins resulting into dysregulation of the adrenal glands affecting the physiological host response (Fig. 7.1). The most commonly linked bacteria with adrenal damage is *M. tuberculosis*. *M. tuberculosis* can reside within adrenal gland without any clinical symptoms for up to 10 years (Kelestimur 2004). In a study conducted on 13,762 patients of tuberculosis, 6% of *M. tuberculosis* affected active patients exhibited adrenal insufficiency (Lam and Lo 2001). *M. tuberculosis* causes adrenal dysfunction through induction of degenerative cells within adrenal cortex (Kelestimur et al. 1994). The radiographic images of adrenal glands also suggests connection between length and tuberculosis activity in the adrenal gland (Kelestimur et al. 1994). Interestingly, reports revealed that treatment with anti-tuberculosis drugs does not ameliorate the condition of adrenal insufficiency (Bhatia et al. 1998). Another species of *Mycobacterium*, i.e., *M. avium* has been reported to cause infection in adrenals of AIDS patients (Glasgow et al. 1985). Although adrenal failure may result due to infiltrative disease; however, it may also occur without any clinical dysfunction (Guenthner et al. 1984). Unfortunately, the exact role of *M. avium* in adrenal destruction has not been explained completely, but its involvement in concomitant infection with cytomegalovirus virus (CMV) has been suggested. Similar to the above studies, bacterial sepsis is reported to produce bilateral adrenal hemorrhage in the case of Waterhouse-Friderichsen syndrome. One of the most frequently occurring bacterium linked with this syndrome is *N. meningitidis* (Bosworth 1979). However, it may also results during systemic infections caused by *Haemophilus influenzae*, *Pneumococci*, *Streptococcus*, *Klebsiella oxytoca*, *Pasteurella multocida*, *Ewingella americana*, and *Capnocytophaga canimorsus* (Doherty 2001; Hamilton et al. 2004; Karakousis et al. 2001; Tsokos 2003; Givner 1998; Hori et al. 1998; Ip et al. 1995; Gertner et al. 1992; McKinney and Agner 1989; Mirza et al. 2000; Morrison et al. 1985; Piccioli et al. 1994). Although these bacteria are considered to be linked with patients with adrenal insufficiency, but their direct involvement in

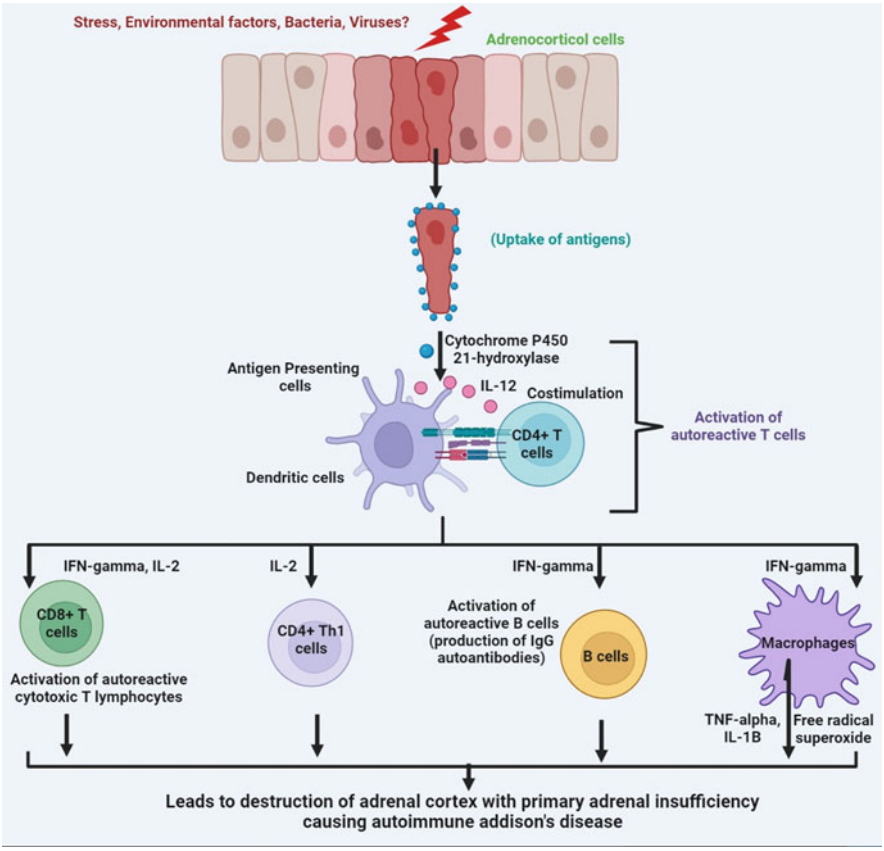

Fig. 7.1 Proposed mechanism for role of microorganisms in autoimmune Addison's disease pathogenesis. Several environmental factors such as stress, bacteria, and viruses have been suggested to contribute in autoimmune Addison's disease (AAD) pathogenesis. In AAD, autoantibodies and autoreactive T cells target cytochrome P450 21-hydroxylase enzyme, as autoantigen. IL-2 and IFN-γ cytokines activate autoreactive T cells (e.g., $CD8^+$ T cells and $CD4^+$ Th1 cells). In addition, IFN-γ activates macrophages and autoreactive B cells which then contribute to destruction of adrenal cortex with idiopathic primary adrenal insufficiency, and lead to autoimmune Addison's disease

AAD is still a mystery. Therefore, further studies are warranted to validate potential role of bacteria in pathogenesis of AAD.

7.2.2 Viruses

Individuals with human immunodeficiency virus (HIV) infection are more susceptible towards several other infections including CMV infection, which results into adrenal dysfunction (Arlt and Allolio 2003; Nakamine et al. 1987; Glasgow et al.

1985; Huang et al. 2004; Angulo et al. 1994; Dore et al. 1995; Rodrigues et al. 2002). However, direct involvement of HIV in adrenal destruction is unusual (Sellmeyer and Grunfeld 1996). Autopsy studies have revealed that in HIV patients, adrenal gland is commonly affected endocrine organ (Welch et al. 1984; Hofbauer and Heufelder 1996). Autopsy study in 128 patients with AIDS showed pathologically compromised adrenal gland within 99.2% of the subjects (Rodrigues et al. 2002). Moreover, adrenal insufficiency was estimated in 5–8% AIDS patients, and it was significantly higher as compared to its incidence in the general population (Huang et al. 2004). Along with direct infection through HIV, other etiological reasons are also stated for adrenal malfunctions which include infections, viral-induced autoimmune deterioration and detrimental effects of chemotherapeutics (Huang et al. 2004). Furthermore, autopsy studies suggest that CMV plays substantial role in adrenal damage in AIDS patients. An adrenal pathology study in AIDS patients reported 21 cases in which adrenal gland was infected with CMV (Glasgow et al. 1985). Although, CMV has the highest involvement in adrenal infection of HIV patients, but antemortem diagnosis remains a rare occurrence (Dore et al. 1995; Eledrisi and Verghese 2001). Disturbance in function of adrenal gland can occur at any stage of HIV infection. Nonetheless, adrenocorticotrophin (ACTH) and cortisol levels occur early in HIV infection, and as HIV infection spreads, the insufficiency occurs with normal to low ACTH levels (Eledrisi and Verghese 2001). Advance HIV infection elevates the cortisol-binding globulin (CBG) within the serum in response to stimulation of adrenal cortex by IL-1β and IL-6 (Mayo et al. 2002). According to several studies, the progression to adrenal failure occurs in advanced HIV infection and the reason considered behind this is co-infection by opportunistic microbes, adrenal burnout, increased peripheral cortisol resistance, and anti-adrenal cell antibodies (Eledrisi and Verghese 2001; Mayo et al. 2002; Salim et al. 1988; Marik et al. 2002). A study conducted on 30 patients with AIDS depicted significant correlation between presence of CMV antigenemia and adrenal insufficiency (Hoshino et al. 1997). Controversy exists as there are no befitting diagnostic parameters for screening and delineating the probable basis for adrenal insufficiency, which majorly holds for some of the variance in number of cases reported (Eledrisi and Verghese 2001).

Moreover, some viruses also exhibit mutagenic potential, particularly Epstein–Barr virus (EBV), which was associated with adrenal gland lymphoma (Ohsawa et al. 1996; Suankratay et al. 2005; Ohshima et al. 1997; Jimenez-Heffernan et al. 1995; Prevot et al. 1994). Surprisingly, adrenal dysregulation of glucocorticoid levels, which is common in HIV patients may substantially promote latent EBV reactivation (Cacioppo et al. 2002). Acute EBV infection can potentially cause adrenalitis (Hertel et al. 1987).

There are also other frequent viruses that have a role in adrenal disease, such as newborn infections with echoviruses, which are linked to deadly disseminated intravascular coagulation, which causes severe damage due to multiple organ damage and adrenal hemorrhagic necrosis (Ventura et al. 2001; Speer and Yawn 1984; Mostoufizadeh et al. 1983; Reyes et al. 1983; Berry and Nagington 1982; Wreghitt et al. 1989). In neonates, Herpes simplex virus (HSV) can potentially cause injury to

the adrenals (Nakamura et al. 1985). According to studies on mice, HSV-1 or HSV-2 causes fast infection of the CNS via adrenal gland (Irie et al. 1987; Hill et al. 1986; Aita et al. 2001). Adrenal glands contain the highest proportion of virus particles of any organ in the early stages of HSV-1 and HSV-2 infections (Potratz et al. 1986). In deadly infections with filoviruses, such as the Ebola virus, colossal apoptotic lysis of cells in numerous organs including liquefaction of the adrenals, has been documented (Mahanty and Bray 2004). Although the Marburg virus has low fatality rate, it can nevertheless harm the adrenal, particularly the cortical cells (Mahanty and Bray 2004; Geisbert and Jaax 1998). Similarly, an arenavirus, Lassa virus is also reported to infect the adrenals (Edington and White 1972). Influenza virus type A has also been suggested to potentially influence ACTH production and its release (Jefferies et al. 1998). The Influenza virus was found to be more fatal in adrenal insufficiency patients (Skanse and Miorner 1959). A study on avian influenza A virus suggests that H5N1 avian Influenza A virus has capacity to cause severe adrenal damage (Lee et al. 2005). The reports for involvement of viruses in adrenal infections are more in comparison with the bacterial involvement. Similar to the studies on bacteria, virus infected adrenal disease reports also fails to provide a direct association with adrenal insufficiency and AAD. Future studies on both animal and human subjects are needed to reach up to any concrete conclusion for the involvement of viruses in AAD.

7.2.2.1 SARS-CoV-2

In addition to the above reported virus infections, recently emerged causative agent of COVID-19 disease, i.e. severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may also be involved in adrenal dysfunction (Ding et al. 2004). However, the cellular abnormalities found in the adrenals could be related to the virus's direct cytopathic effects or systemic inflammatory reactions. Coronavirus can create peptides that are molecular mimics of ACTH, disrupts the host's corticosteroid stress response (Wheatland 2004). Antibodies to viral peptides that bind to both the host's ACTH and the viral protein impair the host's capacity to release corticosteroids, resulting in adrenal insufficiency. Moreover, the use of glucocorticoids to treat coronavirus infection has been proposed as a way to prevent or modify the infection (Wheatland 2004). The COVID-19 was recently exposed to a 19-year-old female with a medical history of Raynaud's phenomenon, and she tested positive for the disease (Bhattarai et al. 2021). The study reported primary adrenal insufficiency due to COVID-19 infection (Bhattarai et al. 2021). The COVID-19 illness and endocrine abnormalities have also been addressed by the European Society of Endocrinology (ESE) (Puig-Domingo et al. 2020). Moreover, a 32-year-old woman with autoimmune polyglandular syndrome type 1 (APS-1) was reported to develop COVID-19. The patient's clinical, immunological and genetic patterns confirmed autoimmune polyendocrinopathy–candidiasis–ectodermaldystrophy (APECED), also known as APS-1 (Betterle et al. 2012; Beccuti et al. 2020). Similarly, a case study on 51-year-old man confirmed with COVID-19 infection exhibited probability of an underlying cortisol deficiency (Hashim et al. 2021). Furthermore, COVID-19 was found in 64-year-old lady with type 2 diabetes and hypothyroidism, who had nausea,

vomiting, and abdominal pain since 1 week. The patient exhibited presence of 21-hydroxylase antibodies, high ACTH level and low cortisol level, indicative of Addison's disease. After infection, the COVID-19 disease might have contributed to rapid, clinically meaningful disease progression. The study suggested that the development of AAD could be linked to a previous COVID-19 infection in the patient (Sánchez et al. 2022).

These case reports offer important insights into the COVID-19 related serious and rare medical conditions including adrenal insufficiency which can be unmasked by SARS-CoV-2 infection; thereby, rendering diagnostic and treatment processes complicate.

7.3 Role of Gut Microbiota in Autoimmune Addison's Disease

The gut microbiota plays a crucial role in shaping activity of the hypothalamus-pituitary-adrenocortical (HPA) axis (Herman et al. 2016). Nevertheless, knowledge on microbiota's effect on adrenals, pituitary, and hypothalamus is scarce (Sudo et al. 2004). The influence of microbiota on the acute restraint stress (ARS) response in the adrenal gland, pituitary, and gut (an organ of extra-adrenal glucocorticoid production) was investigated in a study on germ free (GF) mice (Vagnerová et al. 2019). A study using SPF and GF male BALB/c mice found that the GF mice's plasma corticosterone reaction to ARS was higher than that of SPF mice (Vagnerová et al. 2019). ARS substantially activated the steroidogenic pathway in the adrenals at the levels of the steroidogenic transcriptional regulator Sf-1, cholesterol transporter Star, and Cyp11a1 (the first enzyme in the steroidogenic pathway). These findings show that the gut microbiota influences the adrenals' and microbiota's responses (Vagnerová et al. 2019). Although studies on the HPA axis and the neuroendocrine system have indicated the significance of gut microbiota in modulating adrenal glands, there is no clear indication whether it improves or worsens the adrenal function (Vagnerová et al. 2019; Farzi et al. 2018). So far, there is no study reported on the impact of gut microbiota on AAD. Upcoming research should be more focused on finding the role of intestinal microbiota in AAD and how they can be targeted for improving adrenal functions.

7.4 Role of Probiotics in Autoimmune Addison's Disease

Probiotics have been found to have potential ameliorative benefits in the prevention and treatment of a wide range of systemic diseases in both animal and human investigations. Rheumatoid arthritis, ulcerative colitis, multiple sclerosis, and hepatic encephalopathy are some of the examples of inflammatory and autoimmune disorders in which probiotics have been found useful (Liu et al. 2018). The regulation of immune system function, which is typically reliant on the strain of probiotic bacteria, is one of the major benefits of probiotics. Some strains have been shown to stimulate the immune response, and thereby rendering it beneficial to patients with

immune deficiencies (Ishizaki et al. 2017). Although, previous reports suggested the crucial role of probiotics in ameliorating the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis induced by stress, but there is no report available which directly indicates role of probiotics in benefiting either adrenal complications or AAD (Eutamene and Bueno 2007; Smith et al. 2014). Therefore, future studies should be targeted for exploring the potential of probiotics in improving the adrenal functions in AAD.

7.5 Conclusion

Many organ specific autoimmune diseases including type 1 diabetes have been related to enteroviruses; however, the active involvement of any infectious agents in AAD has yet to be established. The immune system majorly target and coordinately attack on steroidogenic cells of the adrenal cortex by 21OH (one dominant self-antigen), and it is markedly similar to the immune system's attack on viruses, $CD4^+$ and $CD8^+$ T cells, and antibodies specific for an intracellular antigen (Fig. 7.1). In addition, epidemiological research revealed that infections may have a role in the development of AAD. The protracted subclinical phase of AAD, on the other hand, makes it difficult to identify any probable viruses or bacteria that might play a role in the pathogenesis at early stages. Viruses such as CMV, EBV, and HSV-1 are involved in the AAD pathogenesis; however, more extensive research is needed to identify the exact pathomechanisms and other pathogens contributing to AAD. Furthermore, there are no studies that indicate the possible relevance of gut microbiota dysbiosis and probiotics in the treatment of AAD; therefore, animal model and clinical investigations are required. Certain studies, on the other hand, offer potential ways for taking use of AAD's extraordinarily high heritability and gathering a large cohort of families with ADD aggregation (Skov et al. 2017; Mitchell and Pearce 2012). All family members could then be tracked prospectively and examined for evidence of functional adrenal impairment as well as exposure to infectious agents or other environmental factors.

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Part III

Microorganisms in Pathogenesis and Management of Central Nervous System (CNS) Demyelinating Autoimmune Diseases

Microorganisms in Pathogenesis and Management of Multiple Sclerosis (MS)

8

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Abstract

Multiple sclerosis (MS) is a chronic neurodegenerative disorder whose etiology is not fully understood. Genetic factors, environmental factors, and eating habits are involved in the onset and development of the disease. Alterations in the gut microbiota are related to MS development since various studies directly relate it to the immune system and its protection against infections. The complex intestinal microbiota has not yet been fully understood. In particular, dysbiosis has been found in MS, especially in species that produce butyrate, propionate, and

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short-chain fatty acids, among other bacterial products or metabolites. On the other hand, the virome is one of the most studied, especially *Epstein–Barr*, *Herpes Virus, retrovirus, Rubella, and Varicella-Zoster*, some of the most related to multiple sclerosis. This chapter discusses the role of the microbiota and its pathogenesis and management in Multiple Sclerosis.

Keywords

Multiple Sclerosis (MS) · Microbiota · Bacteria · Virus · Microbiome · Virome · Pathogenesis · Inflammation · Immune System

8.1 Introduction

The human gastrointestinal tract is plenty of a large amount of primarily anaerobic bacteria. The gastrointestinal microbiota comprises about 400 species and exceeds the number of cells of all other organs combined, and these "approximately 100 trillion cells" reach a mass of around 1–2 kg in a grown adult (Forsythe and Kunze 2013), roughly the weight of a fully developed human brain (approximately 1.5 kg) (Carpenter and Sutin 1983). It has been estimated that about 90% of cells found in the human body are prokaryotic from about 40,000 bacterial strains in 1800 genera (Forsythe and Kunze 2013; Frank and Pace 2008; Luckey 1972). Considered the "forgotten organ", the gastrointestinal microbiota comprises about 400 species and exceeds the number of cells of other organs combined.

Although the cause of multiple sclerosis (MS) has not yet been determined, genetic, environmental factors, and eating habits have been associated with the onset and development of the disease. A myriad of environmental variables appears to have an impact on MS. Nevertheless, the influence of gut microbiota is believed to have both protective and pathological effects on disease development. Interestingly, several recent findings suggest that molecules produced by the gut microbiota are relevant to the central nervous system (CNS) and can regulate many of its functions (Bennet et al. 2015; Cryan and O'Mahony 2011; Dave et al. 2012; Ochoa-Reparaz et al. 2018; Ortiz et al. 2019).

8.2 Microbiota

The role of gut microbiota has recently become one of the exciting topics in health and disease research. Gut microbiota is highly diverse in origin and number throughout life. Approximately 24–48 h after a shift in location or diet, there are rapid changes to the microbiota composition on a species and family level (but not phyla) (Kolodziejczyk et al. 2019; Vangay et al. 2015; Zhang and Yang 2016). The development of the techniques used for identifying and quantifying the intestinal microbiota has made it possible to better understand its complexity at the functional and populational levels (Moloney et al. 2016).

Multicellular eukaryotic organisms evolved with prokaryotes so that a plethora of different microorganisms are found almost on every surface of the eukaryotic organisms and have beneficial or pathological effects (Dave et al. 2012; Schloissnig et al. 2013; Turnbaugh et al. 2007). Some projects have been designed to study the role of microorganisms in human life: the Human Microbiome Project Consortium (HMP) 2012 (Turnbaugh et al. 2007), the Metagenomics of the Human Intestinal Tract (MetaHIT), (Qin et al. 2010), and the Elder met project. The last project is focused on aging people (Claesson et al. 2012).

The distal intestine of mammals is home to an enriched and highly diverse bacterial ecosystem that includes an essential part of the microbiome. Bacteria have an intimate relationship with their hosts and populate the intestine shortly after birth, possibly even during gestation. The microbiota plays a fundamental role in developing the immune system (IS) since around 70% of the IS resides in the intestine, the degradation of food products, and protection against infections. Most gut microbes live in the lumen of the intestines, lined by cells that form a barrier and interface for host–microbe interactions. The intestinal barrier breakdown causes the intestinal microbes to move to an area where the majority of the intestinal immune cells are found, mainly lymphocytes and macrophages, activating the immune mechanisms.

Furthermore, the gut microbiota plays an essential role in differentiating CD4 helper T-cells and their infiltration into the brain. Therefore, interactions between the gut and microbes are crucial to developing and maintaining host immunity. Dysregulation of the intestinal microbiota can have severe consequences on the host's health (Bennet et al. 2015; Bravo et al. 2011; Chen et al. 2016; Dinan and Cryan 2013; McKernan et al. 2010; Stasi et al. 2012; Uchiyama et al. 2019) (Fig. 8.1).

The gut microbiota can affect its host by reprogramming immune cells, promoting cytokine secretion, producing bacteriophages, and, in some cases, crossing the blood–brain barrier (BBB). The BBB is made up of specialized cells (vascular non-fenestrated endothelial cells, pericytes, and podocytes from astrocytes) that prevent the passage of proteins or other molecules of high molecular weight to the CNS, acting as a regulatory interface between the brain and the blood, and that has a healthy, communicative function. Disruption of tight junctions can lead to the barrier's permeability and expose the CNS to harmful substances (Ortiz et al. 2014). Some bacteria can cross the BBB without alteration, while others require peripheral immune cells' alteration and/or participation. Studies have shown that certain living bacteria can positively influence the BBB, helping to regulate the interaction between the periphery and the CNS (Bermudez-Humaran et al. 2019; Carabotti et al. 2015; Cryan et al. 2020; Ortiz et al. 2014) (Fig. 8.2). Alterations in the functions of the BBB are crucial in the development and progression of MS (Ortiz et al. 2014). Experimental studies in animals suggest that the microbiome affects the development and maturation of the microglia (Bravo et al. 2011; Chu et al. 2018; Desbonnet et al. 2008; McKernan et al. 2010; Neufeld et al. 2011). Bacteria in the gut release factors and metabolites into the blood that can easily cross the BBB or otherwise interact with barrier cells and thus affect the CNS.

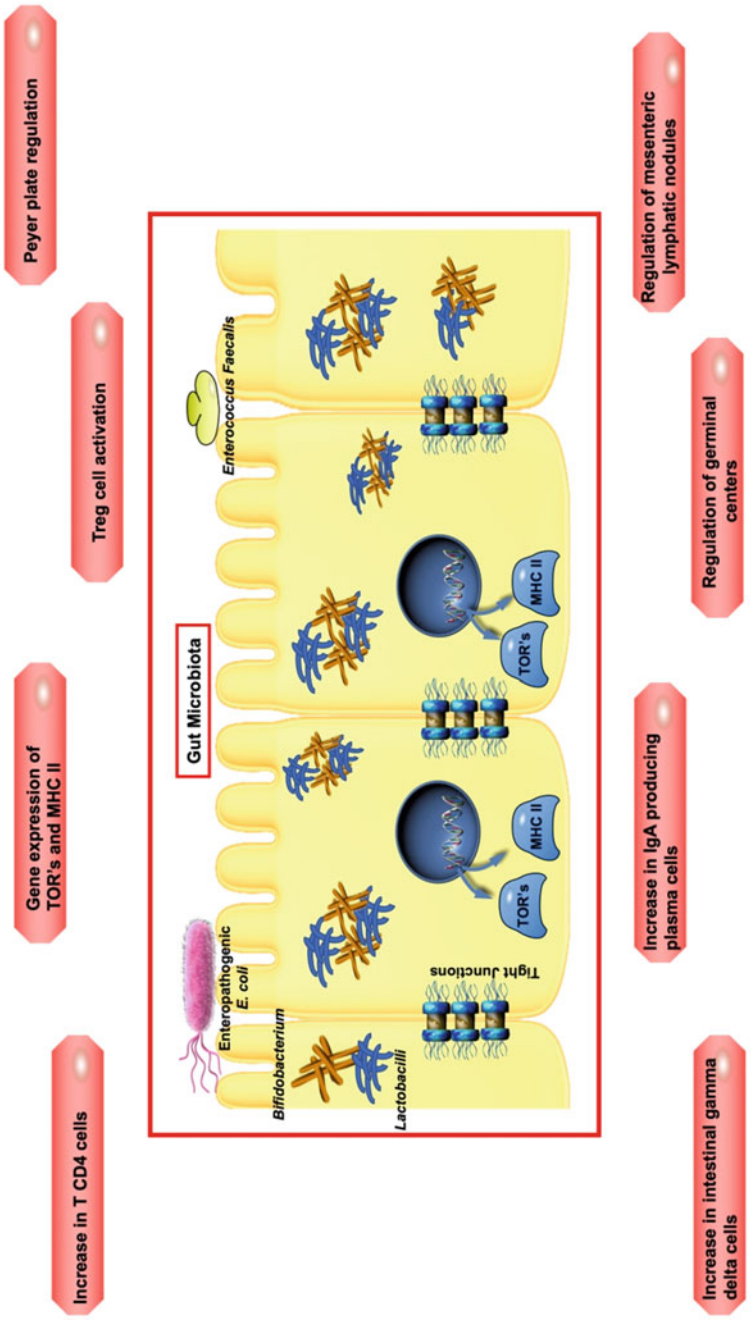

Fig. 8.1 The alteration of the gut microbiota affects multiple routes with final damage to the central nervous system. (*Some pictures were taken from Qiagen Pathways*)

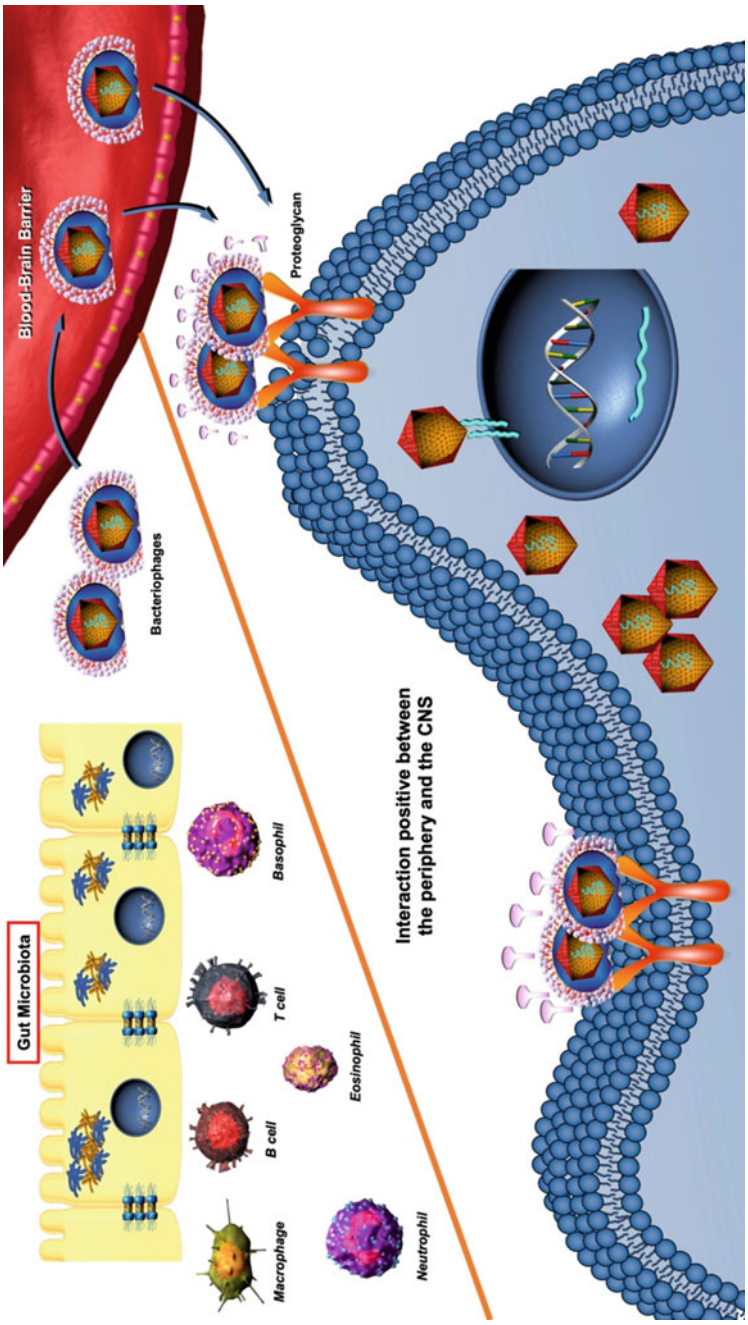

Fig. 8.2 The gut microbiota affects the secretion of cytokines and favors the action of bacteriophages, some of them cross the BBB, which positively influences the CNS and the periphery. (*Some pictures were taken from Qiagen Pathways*)

Communication between the gut and the brain can alter neurological functions and play a vital role in mediating stress-related behaviors such as anxiety and depression (Burnet and Cowen 2013; Desbonnet et al. 2008; Dinan and Cryan 2013; Fond et al. 2015; Forsythe and Kunze 2013; Logan and Katzman 2005; Lyte 2011; Neufeld et al. 2011) (Fig. 8.2).

Experimental studies in animals have shown that an alteration of the intestinal microbiota can lead to various pathologies, both gastrointestinal and outside the gastrointestinal system. Others have shown in animal models that alterations can wildly influence experimental autoimmune encephalitis (EAE) in the intestinal microbiota. It has been demonstrated that the decrease or elimination of the intestinal microbiota leads to the reduction in the intestine and the periphery of the number of CD 4 helper T lymphocytes involved in inflammation (Th17). Thus, the intestinal microbiota and its metabolites have been involved in the pathogenesis of autoimmune diseases that also affect T-cell-induced inflammatory pathology and alteration of the BBB. Studies have examined how the components (or metabolites) resulting from the breakdown of certain foods could influence the expression of MS or modulate the inflammatory response. Taken together, these results suggest a complex interdependence between diet, microbiota, and the IS, that could lead to susceptibility to MS and that the gut microbiome contributes to the inflammatory responses that influence the course and outcome of MS (Bermudez-Humaran et al. 2019; Chu et al. 2018; Cryan et al. 2020; Desbonnet et al. 2008; McKernan et al. 2010; Tankou et al. 2018).

Several studies have compared stool samples from people with MS and healthy controls, which show notable differences in humans. These differences are due to the enrichment of certain bacteria and the change in bacterial species (variation in diversity) depending on the disease and the disease-modifying treatment. The ability to quickly determine an individual's microbiome through non-invasive measurements (collection of fecal samples) could be used as a diagnostic and/or prognostic tool to inform therapeutic strategies (Chen et al. 2016; Claesson et al. 2012; Dave et al. 2012; Dlugosz et al. 2015; Ghaisas et al. 2016; Harmsen et al. 2000; Kouchaki et al. 2017; Malinen et al. 2005; Médicale 2017; Roediger 1980; Sha et al. 2014).

There is evidence that children with MS (under the age of 16, which make up less than 5% of people with MS) have subtle differences in their gut microbiota compared to children who are not ill, suggesting a pro-inflammatory environment; however, the results could be affected by exposure to the drugs. This raises the possibility of an MS microbiome or a fingerprint of intestinal disease inside a medical condition. What remains in question is whether the microbiota may be associated with a risk of relapse. However, it is known that decreasing a specific category of bacteria increases the risk of bouts. A growing body of evidence supports that the gut microbiome contributes to CNS function so that dysregulation could be a causal factor in a wide range of CNS diseases. Although the microbiota is unlikely to be the determining factor in the pathogenesis of MS, it could play an essential role in the progression of the disease.

8.3 Multiple Sclerosis and Gut Microbiota

Dysbiosis in the gut microbiota has been found in individuals with relapsing-remitting (RR) MS compared to healthy individuals. Commensal bacteria have been implicated in triggering demyelination in murine models (Berer et al. 2011). People suffering from MS presented with low concentrations concerning several species, particularly *Bacteroides, Prevotella, Lactobacillus,* and *Clostridium* (Turnbaugh et al. 2007). However, the species of these taxa produce molecules with anti-inflammatory and immunomodulatory properties. On the other hand, microorganisms that produce pro-inflammatory compounds were present in more significant numbers in these individuals. The consequences of this dysbiosis have been demonstrated using stool transplants from individuals with EAE to mice lacking intestinal microbiota, which revealed amplification of symptoms in these mice compared to those that received feces from healthy individuals (Chu et al. 2018). These results show the involvement of the microbiota in MS; nonetheless, it is still too early to understand precisely how the microbiota is involved. Reports have included butyrate producers like *Odoribacter*, *Butyricicoccus, or Ruminococcus,* and propionate producers, like *Bacteroides* or bacteria capable of inducing colonic regulatory T-cells, were diminished (Horton et al. 2021; Miyake et al. 2015; Tobin et al. 2021). There are many contradictory results in specific genus and species implicated in MS; however, the significant reduction of propionate in serum or feces of MS patients is broadly reported (Tobin et al. 2021). As an immunoregulator, the lack of propionate is an essential factor in persistent inflammation in MS patients. Some mouse models and clinical intervention studies show promising results with the propionate dietary supplement (Tobin et al. 2021).

Nevertheless we know that the microbiota has an essential role in the IS and inflammation mechanisms and that it can influence the state of the CNS through the gut–brain axis (Cryan et al. 2019; Ortiz et al. 2019). On the one hand, acting on the intestinal microbiota may result inadjuvant treatment for MS since, through the food, we can influence the microbiota and, at the same time, the IS. Moreover, we know there is no mandatory diet for MS, yet a healthy diet is recommended. A diet higher in fiber (prebiotics), such as the Mediterranean or vegetarian diet, is preferable for the gut microbiota. On the other hand, there are no probiotics or symbiotics designed explicitly for MS, and there has been little research on this topic (Bennet et al. 2015; Claesson et al. 2012; Koenig et al. 2011; Riccio and Rossano 2018; Tannock and Savage 1974; Wu et al. 2011) (Fig. 8.3).

Other studies have exhibited the potential of probiotic bacteria such as *Lactobacillus Plantarum* A7 and *Bifidobacterium animalis* PTCC 16318 or a mixture of *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum* (Bravo et al. 2011; Desbonnet et al. 2008; McKernan et al. 2010; Salehipour et al. 2017). More research studies are needed to support probiotics in the treatment of MS. Furthermore, fecal microbiota transplantation (FMT) has been studied several times in MS.

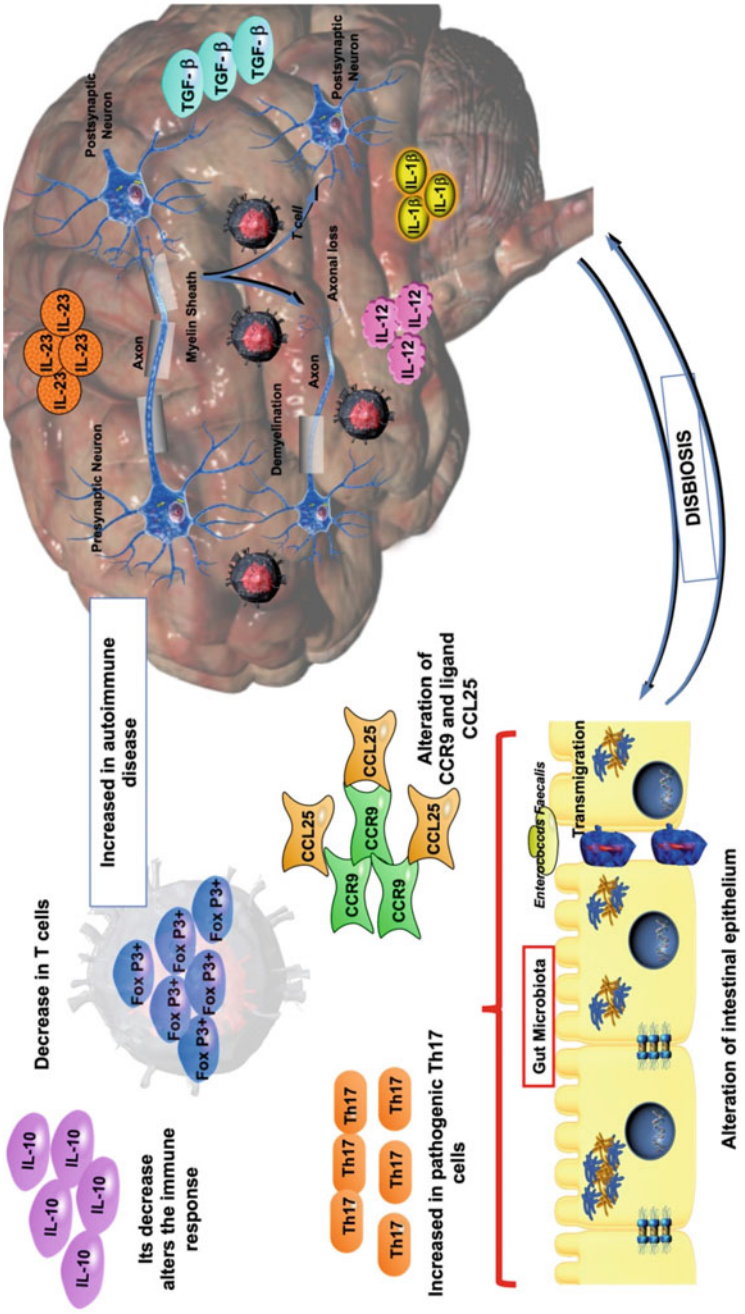

Fig. 8.3 Intestinal dysbiosis affects the development of MS and vice versa; this causes an increase in the pro-inflammatory response and, therefore, demyelination. (*Some pictures were taken from Qiagen Pathways*)

8.4 Multiple Sclerosis, Microbiota, and the Immune System

Multiple sclerosis is a chronic inflammatory disorder that mainly affects the CNS: it is essential to note that although this disease is not fully understood, genetic and environmental factors have been shown to play an important role in susceptibility to suffering MS (Bhargava and Mowry 2014; Chen et al. 2016; Miyake et al. 2015).

The intestinal microbiota represents an essential factor for the cellular and humoral components of the IS in the intestine (Miyake et al. 2015). In turn, the intestinal microbiota plays a crucial role in developing IS. Certain commensal bacteria can induce the synthesis and release of IL-10 (anti-inflammatory cytokine) by regulatory T-cells (Treg), while other bacteria make the maturation of T-helper 17 cells (Th17) possible. The production of Treg cells supports suppressing the immune response towards the same commensal bacteria, while the Th17 cells prepare the organism against an attack by external pathogens (Bhargava and Mowry 2014).

The metabolites generated by the intestinal microbiota exert essential effects on the IS. Colon bacteria produce short-chain fatty acids (SCFAs) by indigestible carbohydrates such as pectins, hemicellulose, and gums. One of the key SCFAs is butyrate, an essential energy source for the colon epithelium. Butyrate can increase the production of cytokines such as IL-4 and IL-10 by monocytes, leading to a state of no-inflammation (Bhargava and Mowry 2014; Miyake et al. 2015). In vitro studies have demonstrated that butyrate reduces the adhesion of leukocytes to vascular endothelium, induces apoptosis of activated T-cells, and inhibits the IFN-g signal transducer. Butyrate can upregulate Tregs-cell populations by signaling G-protein-bound receptors on SCFAs (Bhargava and Mowry 2014, Miyake et al. 2015).

The intestinal microbiota is essential for a variety of immunological functions. In the intestinal barrier, it prevents the colonization and growth of pathogenic microorganisms. It also promotes the maturation of the same barrier by stimulating an innate immune response through toll-like receptors (TLRs), nucleotide-binding and oligomerization domain type receptors (NOD-type receptors), and an intense adaptive immune response. The microbiota plays an essential role in the secretion of mucin, antimicrobial peptides (defensins and cathelicidins), and immunoglobulin-A (IgA) (Castillo-Alvarez and Marzo-Sola 2017). Studies developed in germ-free mice (mice born in germ-free conditions that do not have intestinal flora) have shown that the intestinal microbiota regulates Peyer's patches, mesenteric lymph nodes and centers, and germ cells at the intestinal level. It regulates the number of plasma cells that produce IgA, intestinal gamma-delta T-cells, and CD4 + T-cells of the *lamina propria* or intraepithelial cells and is involved in the gene expression of TLRs and MHC class-II (Castillo-Alvarez and Marzo-Sola 2017).

The intestinal microbiota significantly influences the development and activation of Th17 and Treg cells: these two cell subtypes are involved in the response and regulation of autoimmune processes. Germ-free mice exhibit low levels of Th1 and Th17 cells and an increase in Th2 cells (Castillo-Alvarez and Marzo-Sola 2017; Colpitts et al. 2017; Hindson 2017). This situation is reversible when the mouse is

colonized with normal intestinal microbiota (Castillo-Alvarez and Marzo-Sola 2017). It has been theorized that the microbiota can induce the conversion of Th17cells in a resting state to a state of pathogenic Th17 cells, which occurs when a pro-inflammatory state predominates, promoted by the presence of cytokines as IL-1b, IL-12, IL-23, and TGF-β. It has been observed that a segmented filamentous *bacterium* (SFB) can be sufficient to induce autoimmune activity in a part of Th17 (Castillo-Alvarez and Marzo-Sola 2017; Colpitts et al. 2017).

As mentioned above, the gut microbiota is a crucial factor in the development and function of Treg cells; these cells regulate inflammation caused by microbial stimulation utilizing IL-10 (Castillo-Alvarez and Marzo-Sola 2017). Numerous microbes, such as *Bacteroides fragilis* (specifically polysaccharide-A), have been associated with the induction of Treg cells; *B. fragilis* induces the synthesis and release of IL-10 by FoxP3$^+$ Treg cells, in addition to the fact that it can prevent and resolve experimental colitis processes in rodent models, which demonstrates the role of these cells (Tregs) in the regulation of immune tolerance (Branton et al. 2016; Castillo-Alvarez and Marzo-Sola 2017; Cosorich et al. 2017; Hindson 2017).

The presence and type of bacteria in the gut and brain have been associated with the expression of immune genes in the host. There is an essential interaction between bacteria and host responses through signaling by transcription factors such as NFkB in demyelinating diseases. The signaling pathway through NFkB is critical in neuroinflammation and MS (Castillo-Alvarez and Marzo-Sola 2017; Cosorich et al. 2017*)*. In addition to affecting brain development, the microbiota is also related to autoimmune diseases, autism spectrum disorder, Guillain–Barre syndrome, and disorders such as depression, anxiety, and schizophrenia (Castillo-Alvarez and Marzo-Sola 2017).

The first evidence of the association between intestinal bacteria, peripheral tolerance, and EAE was described by the use of a "vaccine" against an enterotoxic strain of *E. coli*: the "vaccine" in question was composed of a strain of live attenuated *Salmonella typhimurium*, and the mice that received it experienced an attenuated form of EAE, and subsequently fully recovered (Castillo-Alvarez and Marzo-Sola 2017). Histopathological studies revealed a lower inflammatory infiltrate in the spinal cord's gray matter and white matter and a significant decrease in the expression levels of IFN-β secreting T-cells, and an increase in IL-4 levels IL-10, IL-13, and TGF- β. This "vaccine" exhibits anti-inflammatory properties by involving FoxP3$^+$ Treg cells (Branton et al. 2016; Castillo-Alvarez and Marzo-Sola 2017; Colpitts et al. 2017; Cosorich et al. 2017; Hindson 2017).

In MS, immune cells attack the myelin sheaths that cover and protect neurons, and the resulting demyelination and axonal loss lead to paralysis and loss of function (Colpitts et al. 2017). Different forms of MS have been described, with the most common being relapsing-remitting MS (RR-MS), which affects 85% of all patients: 70% of RR-MS patients develop a secondary-progressive form of MS (SP-MS) characterized by axonal loss and brain atrophy, leading to progressive neurological disability (Colpitts et al. 2017). The immunological changes that occur during the different phases of the disease can modify the composition of the intestinal microbiome, and the changes in the microbiome are relevant in the early stages of

the disease; changes that are characterized by the reduction in the abundance of specific genera such as *Lactobacillus* (Colpitts et al. 2017). It has been shown that a mixture of *Lactobacillus spp.* can protect against the severity of murine EAE via the induction of IL-10 producing Treg cells. The *Shirota* strain of *Lactobacillus casei* (LcS) delays the onset and severity of the disease by restoring the Th1/Th2 balance (Colpitts et al. 2017; Mestre et al. 2019).

In MS, the alteration of the commensal microbiota acts as an environmental pathogenic risk factor (Schepici et al. 2019). The gut microbiota is influenced by the interaction between the C-C type-9 chemokine receptor (CCR9) and its ligand, CCL25. This interaction plays an essential role in developing and immunity of T-cells in the intestinal epithelium. An increase or decrease in CCR9 function is observed in patients with RR-MS and SP-MS forms (Schepici et al. 2019). Blocking the CCR9-CCL25 interaction provokes a reduction in $CCR9^+$ $CD4^+$ T-cells in peripheral blood (Branton et al. 2016; Schepici et al. 2019). The $CCR9^+$ memory T-cells (Tmem) are also affected:antibiotic treatment in SPF (specific pathogen-free) mice induces an increase in $CCR9^+$ Tmem cells, which leads to a significant reduction in the severity of EAE (Schepici et al. 2019). These results show that an alteration in the gut-immune system axis induced by dysbiosis is involved in the pathogenesis of MS (Cosorich et al. 2017; Schepici et al. 2019).

In patients with RR-MS, an increase in the *phylum Firmicutes* and a decrease in the *phylum Bacteroidetes* are observed in the small intestine in patients in the relapse phase compared with patients in the remission phase and with healthy individuals. There is also a decrease in the abundance of *Prevotella* and an increase in *Streptococcus mitis* (*S. mitis*) and *Streptococcus oralis*. *Prevotella* generates the propionate, an inflammatory metabolite of SCFAs (Schepici et al. 2019). In addition, a reduced level of *Prevotella* in these RR-MS patients is directly linked to Th17-cell expansion and disease activity. On the other hand, *S. mitis* can induce Th17-cell differentiation at the intestinal level, which increases tissue damage due to autoimmunity (Branton et al. 2016, Schepici et al. 2019). A reduction in the genus *Clostridium* has been demonstrated in patients with RR-MS compared to healthy subjects; this reduction determines a significant decrease in the generation of SCFAs. *Clostridium* is responsible for the production and activation of Treg cells in peripheral compartments and increased IL-10 levels. In these patients, higher levels of *Firmicutes* (*Blautia and Durea*) and *Bacteroidetes* such as *Pedobacteria* and *Flavobacterium* are observed, whereas *Bacteroidetes* that generate *Parabacteroides*, *Bacteroides*, and *Prevotella*, are found at lower levels (Schepici et al. 2019). Commensal *Bacteroidetes* are responsible for producing lipid-654, a ligand of TLR2. The levels of lipid-654 are significantly reduced in MS patients. It has been hypothesized that this lipid regulates immune responses, maintains the expression levels of TLR2, and IFN-β signaling (Farrokhi et al. 2013; Schepici et al. 2019). In addition to the decrease in the abundance of the genus *Bacteroidetes*, a reduction of *Adlercreutzia* is observed in patients with RR-MS. *Adlercreutzia* may be involved in anti-inflammatory responses due to its relationship with the metabolism of phytoestrogens, which are molecules of plant origin with a chemical structure and biological activity like to estrogens. The primary sources of these compounds are legumes, fruits, some grains

Table 8.1 Relationship between gut bacterial genera and immune system in Multiple Sclerosis

	↓*Clostridium*---↓levels of Treg cells, IL-10 and SCFAs
	↑*Firmicutes*---↓inflammatory process
	↓ *Prevotella*---↓ Lipid-654 and IFN-β signaling
MS-gut	↑ *S. mitis*---↑ Th-cells differentiation and proinflammation
	↑ *Methanobrevibacter*--- ↑ IBDs and lymphoid areas in the intestinal mucosa
	↓ *Adlercreutzia*--- ↓phytoestrogens metabolism
	↑ *Akkermansia*---↑pro-inflammatory activity
	↓ *Butyricimonas*--- ↓ butyrate production,↑inflammation,↓ Tregs-cells
	↓*Parabacteroides distasonis*---↓protection

and vegetables. *Adlercreutzia*-type bacteria are responsible, through β-glucosidase, for converting phytoestrogens into monomers. In patients with RR-MS, the reduction in the levels of *Adlercreutzia* reduces the conversion capacity of phytoestrogens, which in turn leads to an increase in oxidative stress and in the levels of inflammatory cytokines such as IL-6 and the chemoattractant protein-1 that are observed very high in MS (Jantaratnotai et al. 2013).

In MS patients, there is an increase in *Methanobrevibacter* (*Euryarchacota phylim*) and *Akkermansia* (*phylum Verrucomicrobia*) and a decrease in the abundance of *Butyricimonas*. *Methanobrevibacter* is distributed in the intestinal mucosa, specifically in lymphoid areas, and has been associated with several inflammatory bowel diseases (IBDs) (Schepici et al. 2019; Tremlett et al. 2016). *Akkermansia* is closely involved in the transformation of mucin to fatty acids, specifically, SCFAs, which, as mentioned above, have significant immunoregulatory effects *(*Schepici et al. 2019). This bacterium may also exhibit pro-inflammatory activity related to its ability to break down mucus; and this mechanism causes damage to the intestinal barrier and exposes resident immune cells to more significant contact with microbial antigens (Ganesh et al. 2013). The pro-inflammatory activities of *Akkermansia* are related to the up-regulation of genes involved in the antigenic presentation, the signaling of B-cell and T-cell receptors, and the activation of complement and the coagulation cascade (Ganesh et al. 2013).

The genus *Butyricimona* produces butyrate, which induces Tregs. In MS, a significant reduction of these bacteria is observed (Castillo-Alvarez and Marzo-Sola 2017; Hindson 2017). The reduction of butyrate in the colon can interrupt the function of the barrier and promote inflammatory processes (Schepici et al. 2019). A significant decrease in the abundance of *Parabacteroides distasonis* has also been demonstrated in patients with RR-MS; and these bacteria play a crucial role in protecting the host of this disease (Jantaratnotai et al. 2013; Schepici et al. 2019) (Table 8.1).

The etiology of MS depends on genetic and environmental factors, eating habits, and lifestyle, which can influence the course of the disease. Diet influences the intestinal bacterial flora composition and indirectly affects the development of inflammatory autoimmune diseases like MS (Amato et al. 2018). Obesity is a significant risk factor for the development of MS, especially in children and

adolescents. The microbiota of obese patients is rich in *Firmicutes* and *Actinobacteria*, also observed in MS patients. Obese individuals show a significant reduction in the presence of *Bacteroidetes* (production of SCFAs), which induce the expansion of Tregs-cell clones. The decrease of *Bacteroidetes* in obese subjects and MS patients leads to an important predisposition to suffer inflammatory processes (Farrokhi et al. 2013, Schepici et al. 2019). Altered microbiota exhibits pathogenic *Firmicutes*, compared to *Bacteroidetes*, which conduce to a breakdown of the microbial balance between the microbiota and the host. This condition favors endotoxemia and acute and chronic inflammation in the intestine, besides increasing the risk of diseases mediated by IS (Brown et al. 2012; Maynard et al. 2012). The chronic inflammation characteristic of MS may be related to body fat since adipocytes can secrete TNF-α, IL-6, and leptin. Leptin is a pleiotropic molecule that regulates appetite and has a crucial impact on the activation and migration of neutrophils, macrophages, and monocytes (La Cava and Matarese 2004; Matarese et al. 2005; Schepici et al. 2019). An increase in leptin levels in the early stages of MS leads to a reduction in the population of Treg cells and an increase in effector T-cells, switching the response phenotype to an inflammatory-type response, typical in autoimmune diseases (La Cava and Matarese 2004; Matarese et al. 2005).

Vitamin-D deficiency is a potential risk factor for MS (Schepici et al. 2019). The distribution of the prevalence of MS depends on latitude and has been associated with the intensity of sunlight and serum vitamin-D levels (Di Rosa et al. 2011). This vitamin is considered a potent immunomodulatory molecule that plays an essential role in innate and adaptive immunity processes (Di Rosa et al. 2011). Vitamin D has direct and indirect effects on T-cells; and it has also been determined that the risk of developing MS is correlated with serum levels of 25-hydroxyvitamin D3 (25-(OH) -D), the biologically inactive form for storing vitamin D (Munger et al. 2006). Vitamin D is capable of inhibiting the synthesis and release of IFN-γ, in addition to being involved in the regulation of gastrointestinal homeostasis by activation of innate immune responses and the induction of Treg cells. Vitamin D maintains the healthy composition of the intestinal microbiota and promotes the integrity of the epithelial cells. At the brain level, vitamin D is involved in normal brain development via the regulation of neurotrophic factors (Holick 2015). Specifically, in MS, it has been concluded that exogenous administration of vitamin-D3 can improve the course of the disease (Schepici et al. 2019).

8.4.1 Smad7 Protein

Although the gut microbiota was long suspected of playing a role in EAE, the Smad7 protein has been studied as it mobilizes immune cells in the gut, causing inflammation of the central nervous system (Hu et al. 2021). Studies on EAE, and human tissue samples from affected patients, have identified the action of these signal proteins (Smad7) on intestinal T-cells in mice. Then, the symptoms of mice genetically modified to have exceptionally high levels of Smad7 in T-cells, or deprived of Smad7 in their T-cells, were compared with those of healthy (normal) mice. Marked

EAE-like clinical symptoms appeared in animals with an elevated level of Smad7 in T-cells. In the intestines of these animals, T-cells are more frequently activated and migrate to the CNS, where they induce inflammation. The relationship between protective regulatory T-lymphocytes and autoreactive and pathogenic T-lymphocytes is modified. In contrast, in Smad7-free mice, no clinical signs of EAE were observed (Abarca-Zabalia et al. 2020; Kleiter et al. 2010).

These experimental results are confirmed in patients with MS by analyzing intestinal tissue samples from MS patients compared to samples taken from healthy controls. Changes similar to the experimental model were observed in humans: the signal protein Smad7 is present more frequently in intestinal mucosa samples from affected patients than from healthy controls. Likewise, the pathogenic mechanisms outweigh the regulatory mechanisms in intestinal mucosa samples from affected patients (Haupeltshofer et al. 2019; Zhang et al. 2018).

It has been suggested that the Smad7 protein is a promising therapeutic target for developing treatments for other autoimmune diseases, including Crohn's disease and other chronic inflammatory bowel diseases. These results suggest that the same is true for MS. Beyond that, the involvement of the intestine is confirmed in the development and progression of MS.

8.5 Viruses and Multiple Sclerosis

The involvement of viral agents in MS has been suggested by detecting viral nucleic acids, proteins, or antiviral antibodies in the blood, cerebrospinal fluid, and brain tissue of these patients. Several viruses have been associated with MS, although a definitive cause-and-effect relationship has not yet been established. Although no specific virus capable of causing the development of MS has been found so far, research has continued based on a series of epidemiological and laboratory data. Due to the complexity and heterogeneity of MS, more than one viral agent may be involved (Cusick et al. 2013; Donati 2020; Tarlinton et al. 2019; Virtanen and Jacobson 2012).

The ubiquitous viruses that make up the microbiome are called viromes; these could challenge and shape the IS in a similar and/or complementary to the microbiome.

8.5.1 Epstein–Barr Virus

Epstein–Barr virus (EBV) seropositivity in the world population is approximately 95%, while almost 100% of patients with MS are EBV-positive. Also, a history of mononucleosis significantly increases the risk of developing MS. Contrary to unequivocal serological data, the search for EBV in the brains of patients with MS produces conflicting results, concluding that there is no clear evidence of the responsibility of EBV infection in causing MS. It has been hypothesized that EBV induces memory B cells to act against a CNS epitope. In addition, a two-shot

hypothesis has been formulated to explain the association of EBV infection with MS: during primary infection, EBV alters the permeability of the BBB, allowing activated immune cells to enter the CNS, thus generating a cascade of events that lead to inflammation of the CNS. In addition, it is shown that sera from patients with MS, unlike healthy controls, recognize unique epitopes of the EB nuclear antigen (EBNA) 411–426 with antibodies that cross-react with myelin basic protein (MBP) (Jog et al. 2020; Pakpoor et al. 2013).

Furthermore, SJL/J and Balb/c mice injected with the peptide EBNA 411–426 develop signs of EAE. This allows us to better understand the possible role of EBV through molecular mimicry in the pathogenesis of EBV multiple sclerosis.

8.5.2 Human Herpesvirus 6

An association of human herpesvirus-6 (HHV-6) with MS was suggested in 1993 and has concentrated many studies. Two species of HHV-6 are known, namely HHV-6 A and HHV-6 B, which share 95% homology. The HHB-6 B accounts for most symptomatic infections during childhood, including rash *subitum* (or *roseola infantum*). The prevalence of HHV-6A (currently not associated with a specific disease) is unknown due to the cross-reactivity of HHV-6A and HHV-6 B antibodies; however, early studies have documented a higher detection rate of HHV-6A in cerebrospinal fluid (CSF), compared to peripheral mononuclear cells in the blood (Ablashi et al. 2014).

Viral DNA can integrate into host cell chromosomes, with a prevalence of approximately 0.85% in the general population, and neural cells can be a site of latency. An association between HHV-6 and MS has been demonstrated, both by direct detection of DNA in typical MS lesions and by finding an increase in antiviral antibody titers in patients with sclerosis; and it has also shown a sequence homology between the HHV-6 U24 protein and the MBP, which suggests a mechanism of molecular mimicry (Hall et al. 1998; Merelli et al. 1997; Pellett et al. 2012; Sola et al. 1993).

To enter cells, the HHV-6 virus uses the complement regulatory receptor CD46, expressed in adult oligodendrocytes, astrocytes, and microglial cells, responsible for viral neurotropism, and the expression of the HHV-6 antigen is upregulated in the typical lesions of autoimmune encephalitis, similar to what is seen in MS. There is also a decrease in naive CD8 cells with the peripheral expansion of memory/effector $CD8^+$ cells related to the duration of autoimmune encephalitis. In light of these findings, we know that HHV-6 could activate the IS, creating a *fertile field* for expanding autoaggressive T lymphocytes (Challoner et al. 1995; Santoro et al. 1999).

8.5.3 Human Endogenous Retroviruses

Millions of years ago, human endogenous retroviruses (HERV) were incorporated into the human genome. The presence and/or activation of three HERVs (HERV H, HERV K, and HERV W) have been associated with MS. The results suggest that

HERV activation could trigger a demyelination process, contributing to MS progression. The HERVs can be activated by several mock viruses, including varicella-zoster virus, HSV-1, EBV, and HHV-6; however, the most studied association is with EBV. The activation of the HERV W MS-associated retrovirus (MSRV) during infectious mononucleosis suggests that the activation of MSRV could induce the development of MS. Again, this viral interaction would be following the theory of a *fertile field* created, in this case, by a previous EBV infection (Arneth 2018; Kury et al. 2018; Mameli et al. 2013; Morandi et al. 2017).

8.5.4 Measles, Rubella, and Varicella-Zoster Viruses

The most common component of the polyspecific intrathecal humoral response in patients with MS has been the measles, rubella, and varicella-zoster viruses. Additionally, several studies have shown that infection caused by the chickenpox virus is associated with an increased risk of developing MS; however, there is a lack of appropriate animal models for studying its role in MS. The role of viral infections in MS has not yet been defined. The possibility that more than one virus is involved in its pathogenesis must be taken into account.

Furthermore, the possible degrees of interaction between viruses and other infections or environmental and genetic factors could vary significantly, which is consistent with the heterogeneity of MS. The detection of viral components in typical disease lesions, or antiviral immune responses in patients with MS-associated with clinical relapses, is highly indicative of the role viruses may play, possibly as triggers or cofactors in the development of the disease. However, these viruses' ubiquity and human specificity make it challenging to study possible mechanisms (Kang et al. 2011; Mahalingam et al. 2019) (Fig. 8.4).

8.6 Probiotics and Multiple Sclerosis

Studying the possible relationships between the microbiota and MS is a new but rapidly expanding field. Understanding the underlying mechanisms related to the progression and development of MS could pave the way for new treatments through modification of the composition of the microbiota using specific strains of microorganisms with anti-inflammatory and protective action. Probiotics, administered orally in adequate amounts, would prevent the spread of the cascade of inflammatory events responsible for the processes of demyelination and cellular degeneration underlying the disease. Some of these products contain various species of *lactobacilli*, which have been shown to prevent autoimmune diseases and are therefore potentially useful for the treatment of multiple sclerosis. Other probiotics with therapeutic effects contain strains of the *genus Clostridia*, capable of promoting the proliferation of lymphocytes with regulatory activity (Cox et al. 2021; Tankou et al. 2018).

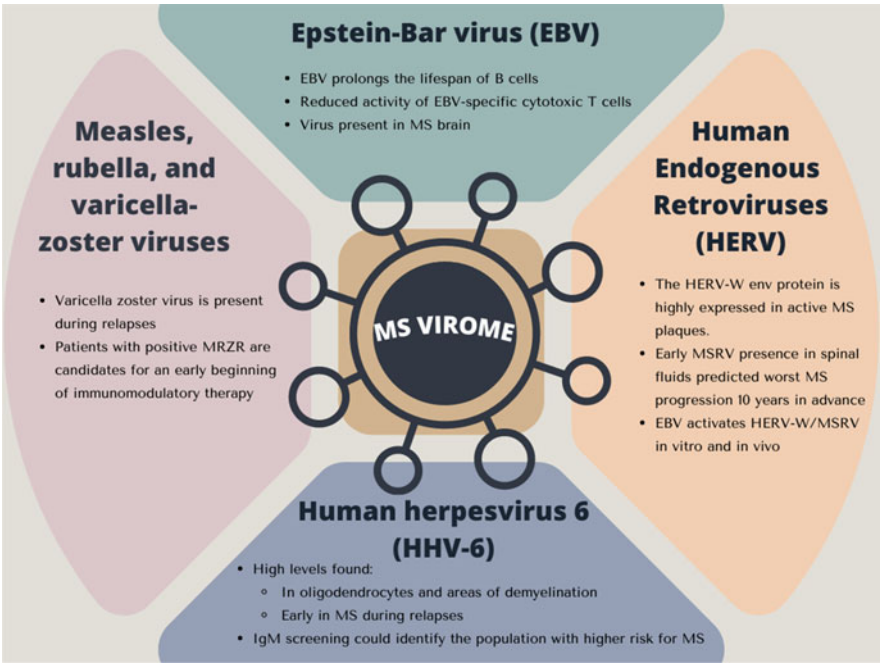

Fig. 8.4 Summary of evidence of the main viruses associated with Multiple Sclerosis. (Abbreviations: MS: Multiple Sclerosis; MSRV: Multiple Sclerosis-associated Retrovirus; MRZR: Measles, Rubella, Varicella-Zoster Virus-reaction)

The probiotic supplement based on *Lactobacillus*, *Bifidobacterium,* and *Streptococcus* (LBS) has positive synergistic effects with drug therapy for the relapsing-remitting form of multiple sclerosis by intervening in intestinal dysbiosis and promoting a correct immune response. It has shown the participation of the intestinal bacterial component in multiple sclerosis. For instance, the alpha diversity values expressing bacterial biodiversity decreased in the control group after LBS treatment. At the same time, no significant differences emerged from the samples of subjects with multiple sclerosis. Regarding the structure of the microbiome, expressed in terms of beta diversity, a modification was found in both groups despite not reaching statistical significance in patients with multiple sclerosis. In addition, after discontinuation of the probiotic, the structural changes tend to return to the initial situation in all subjects. Analysis of the relative abundance of microorganisms emerged that the introduction of LBS leads to an increase in the *Veillonellaceae* family and the *Collinsela* genus in the control group, which are not present in individuals with multiple sclerosis. The LBS probiotic mixture was also associated with a diminution in the profusion of the genera *Akkermansia* (Th1 inducer), *Blautia*, and *Dorea,* which are commonly found in multiple sclerosis patients.

On the other hand, this probiotic mixture can reduce the activity of many metabolic pathways, including some altered precisely in multiple sclerosis

conditions, such as the pathway of porphyrin and chlorophyllin or methane metabolism. The metabolic structure then revealed an increase in the concentration of uracil, adenosine monophosphate, hypoxanthine, and xanthine in controls after LBS, while in patients with multiple sclerosis, the levels of 2-oxoglutarate combined with a decrease of 3-hydroxyvalerate. Discontinuation of the probiotic mixture resulted in the growth of 3-methyl-isovalerate, citrate, nicotinate, and alpha-ketoisovalerate in subjects with multiple sclerosis and 2-oxoglutarate in controls. Furthermore, the relative frequency of Th17 and Th1 lymphocytes decreased, and there was also an effect on other immune system cells. Although these studies are preliminary, it is imperative to analyze these data more extensively and systematically. There is nothing to lose and everything to gain by rebalancing the microbiota in MS patients; this involves taking probiotics and other dietary interventions (Cox et al. 2021, Tankou et al. 2018).

Not all probiotic supplements are the same; it is imperative to choose a product that contains *Lactobacilli* and/or *bifidobacteria* in variable amounts depending on the strain used, but always higher than 1 billion CFU per day per probiotic and up to 20 billion for all. The desirable duration of intake is at least 8 weeks. When taking probiotics, it is also necessary to increase the proportion of prebiotics in the diet to nourish the good bacteria and promote their implantation in the intestine.

8.7 Conclusion

This work demonstrates that MS is an autoimmune disease with many other factors that will influence your disease course, and it is still debatable who, where, and how it started. In a previous work (Ortiz et al. 2020a, b), we showed that the role of the glia and the electrophysiological activity happens before the immunological cascade since there are no immune cells present in the CNS during the early stages of MS, and especially when the lesions first appear. Only the deterioration of the BBB (Ortiz et al. 2014) and the death of the oligodendrocytes (Ortiz et al. 2020b) can be observed, which means that we must look beyond autoimmunity for the cause of the initial deterioration of tissues; for example, to the intestinal microbiota (microbiome and virome) and its relationship with immune-mediated inflammatory diseases.

The combined use of modern genome sequencing protocols illustrates how advanced technologies can generate information that will help better understand and address health problems with a holistic outlook (Hill et al. 2014; Dave et al. 2012; Zhu et al. 2010; Turnbaugh et al. 2007; Médicale 2017). Immune-mediated inflammatory disease (IMID) involves common inflammatory pathways, but otherwise, they appear unrelated and have no known cause. The human microbiome is believed to influence human hormonal, metabolic, and immune functions. Thus, alterations in the diversity of the human intestinal microbiome could be associated with pathological conditions. These changes have been observed in patients with MS, but it is unclear if this phenomenon is a cause or an effect of the disease (Stasi et al. 2012; Harmsen et al. 2000; Branton et al. 2016; Calvo-Barreiro et al. 2018;

Brown et al. 2012; Riccio and Rossano 2018; Miyake et al. 2015; Bermudez-Humaran et al. 2019; Macpherson and Uhr 2002; Bhargava and Mowry 2014; Ochoa-Reparaz et al. 2018; Ghaisas et al. 2016; Cryan et al. 2020; Sommer and Backhed 2013).

Using microbial differential abundance analysis and machine learning (two different but complementary analytical methods), several significant differences were found between the gut microbiota of IMID patients and its control subjects; specifically, the genera *Actinomyces*, *Eggerthella*, *Clostridium* III, *Faecalicoccus*, and *Streptococcus* were considerably more profuse in all of the patients compared to healthy subjects. This data agrees with other studies showing the role of the intestinal microbial community in inflammatory pathologies (Farrokhi et al. 2013; Salehipour et al. 2017; Wong et al. 2006; Bermudez-Humaran et al. 2019; Ghaisas et al. 2016; Zhu et al. 2010; Turnbaugh et al. 2007; Roshchina 2016; Desbonnet et al. 2008; McKernan et al. 2010; Tankou et al. 2018). From a public health perspective, increasing the abundance of species that confer host-specific health benefits and/or decreasing the profusion of species with established pathogenicity, could pave the way for new treatment options.

In recent years, sufficient experimental evidence has accumulated that has demonstrated the role of microorganisms and nutrition in contact with the intestinal mucosa in the onset and development of multiple sclerosis. An alteration in intestinal microbiota composition is observed through the stages that precede reactivation of the disease in MS. That change leads to the proliferation of inflammatory lymphocytes that, after passing through the BBB and reaching the central nervous system, can trigger a whole series of cascading inflammatory events, with concomitant demyelination events. It has been suggested that it is possible to reduce the appearance of exacerbations in patients with multiple sclerosis through therapeutic interventions with dietary probiotics, which have anti-inflammatory effects. The intake of prebiotics may also favor the growth of microorganisms such as *Lactobacilli*, *Bacteroides fragilis,* and *Prevotella*. Further studies will be needed to provide patients with precise dietary indications or suggest nutritional supplements and probiotics in association with the administration of current therapies and immunomodulatory factors to diminish the incidence and severity of relapses and the progression of MS-related disability.

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9 Microorganisms in Pathogenesis and Management of Guillain–Barré Syndrome (GBS)

Navneesh Yadav, Pragati, and Mitesh Kumar Dwivedi

Abstract

Guillain–Barré syndrome (GBS) is an autoimmune disorder of the peripheral nervous system encompassing clinically heterogenous group of diseases such as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and others. Genetic aetiology of GBS remains unknown till today but in most cases is often triggered by a preceding microbial infection or vaccine in few instances. Recent studies have suggested an association of GBS with recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections; however, the underlying mechanism remains undetermined. Massive vaccination drives carried out in the world for COVID-19 disease have also raised few concerns on the overall risk–benefit ratio regarding the development of GBS following vaccination. Molecular mimicry is the most commonly accepted immunopathogenic mechanism in GBS for infections including SARS-CoV-2; however, they do not explain all the cases. Impairment in the gut–brain axis due to altered gut microbiota has been linked to various neurological disorders, and with the close connection of immune system with gut microbiome, the development of GBS following gastrointestinal infections can be explained. This can facilitate the development of microbiome-targeted therapies such as prebiotics and probiotics together with immunotherapy for GBS management.

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Guillain–Barré syndrome (GBS) · SARS-CoV-2 · Gut microbiota · Probiotics · Prebiotics

9.1 Introduction

Guillain–Barré syndrome (GBS) is a rare autoimmune disorder of peripheral nervous system often triggered by an acute microbial infection (Shoenfeld et al. 1996). The peripheral nervous system (PNS) includes all of the nerves that branch out from the brain and spinal cord and extend to other parts of the body—senses, muscles and organs. PNS is divided into two parts: somatic nervous system which is responsible to carry sensory and motor information to and from central nervous system (CNS) and autonomic nervous system that regulates involuntary body functions such as heartbeat and blood flow. GBS is the most frequent cause of acute flaccid paralytic neuropathy where patients develop a range of symptoms that include weakness, numbness and tingling sensations in the arms and legs which can lead to paralysis in severe condition (Goodfellow and Willison 2016; Van Doorn et al. 2008). The clinical features were first described by Landry in 1859, but during World War I in 1916, French neurologists, Georges Guillain and Jean Alexandre Barre, together with physician Andre Strohl, performed detailed clinical diagnosis on two soldiers who developed acute paralysis with areflexia. They found increased protein concentration with a normal cell count in their cerebrospinal fluid, which are the hallmarks of GBS (Burns 2008; Wijdicks and Klein 2017). Based on population surveys, the incidence ranges from 0.4 to 4 cases per 100,000, with slightly more males affected than females. Although GBS is known to occur at all ages; however, due to increased risk of virus infection and compromised immunity, there is a minor peak among young adults and aged people. GBS was initially considered as a single disorder, but based on recent findings, it is a syndrome which includes acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor-sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN) that differs in aetiologies and pathophysiologies but share a common feature of autoimmunity (Kuwabara 2004).

Autoimmunity is a self-damaging immune effector response manifested in various autoimmune diseases such as GBS, where immune cells destroy healthy body cells by mistake. In 50–70% cases of GBS, the symptoms appear 1–2 weeks after a respiratory or gastrointestinal infection or another immune stimulus which results in autoimmune response targeting PNS (Van den Berg et al. 2014b). Both cellular (T-cells) and antibody (B-cells) arms of immunity along with complement proteins and pro-inflammatory cytokines are involved in pathogenesis of GBS. Molecular mimicry between antigens present on microbes and peripheral nervous tissue is one of the most plausible mechanisms for GBS which is triggered by preceding

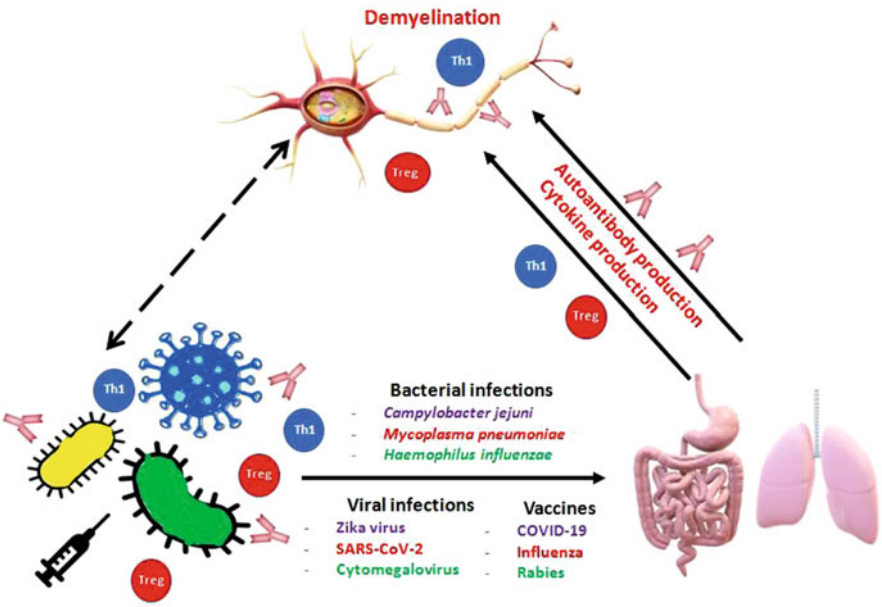

Fig. 9.1 Mechanism of microbial infection/vaccine-induced Guillain–Barré syndrome with possible involvement of gut–brain axis. GBS is a rare autoimmune neurological disease often triggered by upper respiratory or gastrointestinal illness caused by bacterial and viral infections or vaccines in few instances. Immune system produces antibodies and cytokines to protect from infection but also damage body's own nerves by mechanism known as molecular mimicry. Recently, gut microbial alteration, also known as dysbiosis, is emerging as new pathological mechanism for GBS and other related autoimmune diseases

microbial infections (Ang et al. 2004). However, new mechanisms involving antibody class switch and gut–brain axis are emerging (Fig. 9.1).

This chapter is focused on GBS pathogenesis, both microbial and vaccine induced, along with newer insights into gut–brain axis and management of GBS by immunotherapy, probiotics and prebiotics.

9.2 Microorganisms in the Pathogenesis of Guillain–Barré Syndrome

In most cases, the pathogen responsible for the onset of clinical symptoms is unidentified, but serological studies have shown the presence of a pathogen in GBS patients (Shahrizaila et al. 2021). A number of bacteria, viruses and protozoans mentioned in Table 9.1 have been associated with GBS, and the most common ones are described below in the following subsections.

Table 9.1 List of microorganisms involved in the pathogenesis of Guillain–Barré syndrome

Type of microorganisms	Name of pathogen involved in Guillain–Barré syndrome	Reference
Bacteria	– *Campylobacter jejuni*	Rhodes and Tattersfield (1982)
	– *Mycoplasma pneumoniae*	Kusunoki et al. (1995)
	– *Haemophilus influenzae*	Mori et al. (1999)
	– *Helicobacter pylori*	Moran and Prendergast (2001)
Virus	– Herpes simplex virus	Gerken et al. (1985)
	– Varicella zoster virus	Sanders et al. (1987)
	– Hepatitis A and B	Tabor (1987)
	– Cytomegalovirus	Visser et al. (1996)
	– Epstein–Barr virus	Corssmit et al. (1997)
	– Human immunodeficiency virus	De Castro et al. (2006)
	– Dengue virus	Chen and Lee (2007)
	– Chikungunya virus	Wielanek et al. (2007)
	– Hepatitis E virus	Woolson et al. (2014)
	– Zika virus	Cao-Lormeau et al. (2016)
	– SARS-CoV-2	Kamel et al. (2021)
Protozoa	– *Leishmania*	Fasanaro et al. (1991)
	– *Plasmodium falciparum*	Wijesundere (1992)
	– *Plasmodium vivax*	Kanjalkar et al. (1999)
	– *Paragonimus westermani*	Yang et al. (2015)

9.2.1 Bacterial Infections

Campylobacter jejuni is a Gram-negative, non-spore-forming bacterium with spiral shaped morphology responsible for causing gastroenteritis in humans. The transmission to humans is by direct contact with pets or by oral route by ingesting uncooked poultry, contaminated milk and water (Altekruse et al. 1999). Interestingly, it is the most frequent antecedent pathogen for GBS, especially the AMAN form (Hughes and Rees 1997). In 1982, the link between *C. jejuni* and onset of GBS was first documented, where a 45-year-old person developed GBS with irreversible neurological damage following gastroenteritis infection (Rhodes and Tattersfield 1982). Since then, a number of studies have supported the link between them; now with *C. jejuni* involved in 30% of GBS cases worldwide (Nyati and nyati 2013). Following infection in humans, the immune system is activated which results in the production of antibodies against the bacteria. However, due to antibody cross-reactivity with gangliosides present on peripheral axons, the immune system mistakenly attacks the neurons resulting in the disease manifestation. Lipopolysaccharides (LPSs) are a class of lipids containing carbohydrate residues found in the outer membranes of Gram-negative bacteria such as *C. jejuni*, which mimics a wide range of mammalian glycans, present on neurons. Serum samples collected from patients contain antibodies developed against many gangliosides such as, GM1, AsialoGM1, GM1b, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, LM1, GalC and sulfated glucuronyl paragloboside (Yuki 2012). A cascade of inflammatory response is initiated, which involves multiple immune cells such as T-lymphocytes,

monocytes and various cytokines (Hagen and Ousman 2021). Molecular mimicry unfortunately does not explain many observations as not all *C. jejuni*-infected people develop GBS although they have ganglioside-like structure on bacteria (Sheikh et al. 1998), suggesting other mechanisms involving host susceptibility factors may be important.

Mycoplasma pneumoniae is another antecedent bacterial pathogen for GBS. It is a Gram-negative, pleomorphic bacterium with spiral shaped morphology responsible for causing upper respiratory tract infections in humans. It spreads from person-to-person contact by respiratory droplets (Waites and Talkington 2004). The link between *M. pneumoniae* and GBS was first documented in 1995 wherein the patients had developed autoantibodies against galactocerebroside (GalC) which is present in myelin sheaths of both central and peripheral neurons (Kusunoki et al. 1995). These antibodies are also known to react with bacteria, suggesting molecular mimicry as plausible causation of infection (Kusunoki et al. 2001). Interestingly, in a recent study, the antibodies generated in GBS patients were of the isotype IgG and not IgM which are usually present in patients infected with only mycoplasma but does not develop GBS. Therefore, it is proposed that class switching mechanism of antibodies is a critical step in the development of GBS and other autoimmune diseases (Rodríguez et al. 2018).

Recently, a 38-year-old GBS patient was diagnosed with an active yersiniosis and past chlamydiosis; however, it was not clear whether *Yersinia enterocolitica* and/or *Chlamydia pneumoniae* were responsible for GBS for which future animal model studies will be required (Bucurescu 2018). Furthermore, association of *Haemophilus influenzae* with AMAN form of GBS has been suggested with the presence of autoantibodies against GM1 and GQ1b; however, the information is very limited (Mori et al. 1999, 2000). Interestingly, dysregulation of gut–brain axis due to altered gut microbiota facilitated by *Helicobacter pylori* (which is known to cause a wide spectrum of gastrointestinal impairments) has been shown to be associated with GBS, suggesting a newer mode of disease transmission (Moran and Prendergast 2001; Baj et al. 2021).

9.2.2 Viral Infections

Several viral infections have been suggested to play a role in etiopathogenesis of GBS (Table 9.1). Cytomegalovirus (CMV) is a common herpes virus causing mild illness but occasionally can result in hepatitis. The transmission is through body fluids such as saliva, urine, blood and breast milk (Britt 2008). It is the most common viral pathogen involved in AIDP form of GBS, especially common in young female patients. The first association of CMV infection and GBS was made in 1966 (Visser et al. 1996) and later based on large case–control studies; it was found that ~2 cases per 1000 cases of primary CMV infections developed GBS. The patients frequently developed cranial nerve palsies and sensory impairment, dissimilar to what is seen in *C. jejuni*-related GBS patients, suggesting a different mode of disease pathogenesis (Lunn and Hughes 2011). The virus envelope contains a number of glycoproteins

which shares similarity with that of peripheral nerves, and antibodies against GM2 and GalNAc-GD1a have been identified in patients, though the role of GM2 is debatable.

Furthermore, viruses such as Epstein–Barr virus (EBV) (Corssmit et al. 1997), hepatitis E virus (HEV) (Woolson et al. 2014), Zika virus (ZIKV) (Cao-Lormeau et al. 2016) and others (Table 9.1) have also been associated with axonal degeneration and demyelination (Wang 2018); however, their roles in GBS development remains unclear due to unidentified autoantibodies or autoreactive T cells in GBS patients following these viral infections. For EBV involvement in GBS development, a similar mechanism that of CMV has been suggested due to increased serum levels of T-cell activation and migration associated molecules (Hadden et al. 2001). Moreover, a case–control study reported 10% antecedent EBV infection in GBS (Jacobs et al. 1998); however, the exact role of EBV in GBS is still unclear due to limited and controversial findings. In addition, it has been reported that 7.5% of HEV-infected patients exhibit neurological disorders, including brachial neuritis, vestibular neuritis and GBS (Woolson et al. 2014). Moreover, GBS patients showed the presence of HEV genome and anti-HEV IgM antibodies in their blood, suggesting that active HEV infection could still be affecting the autoimmune response at the time of neurological onset and that giving antiviral drugs to patients would be effective treatment strategy for GBS (Van den Berg et al. 2014a, b; Stevens et al. 2017).

ZIKV involvement has been suggested in GBS patients as ~31% cases of GBS patients infected with zika virus had anti-glycolipid antibodies: asialo-GM1 (19%) and GD1a (12%) (Cao-Lormeau et al. 2016). However, previous ZIKV-related GBS was considered as an acute inflammatory demyelinating polyneuropathy (Uncini et al. 2017). Moreover, a study on ZIKV-related GBS suggested that 48% GBS patients exhibited neurological symptoms during or immediately after showing ZIKV infectious symptoms, and CSF samples were found positive by PCR for ZIKV presence (Parra et al. 2016). These studies indicate that ZIKV-related GBS is mediated by para-infectious processes including the direct viral invasion of neural tissues. Recent emergence of Coronavirus disease 19 (COVID-19) pandemic due to SARS-CoV-2 has also resulted in other immunological complications including GBS, and the link between SARS-CoV-2 and GBS is discussed below.

9.2.2.1 Link Between SARS-CoV-2 and Guillain–Barré Syndrome

COVID-19 caused by the spread of 2019 novel coronavirus (2019-nCoV), responsible for the death of millions, was declared a pandemic by the World Health Organization. This virus was named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as it shared ~80% homology with previously known SARS-CoV, which caused acute respiratory distress syndrome (ARDS) during 2002–2003. Another virus, which shares the homology, is Middle East respiratory syndrome coronavirus (MERS-CoV), and it also caused respiratory illness (Singhal 2020; Sharma et al. 2021). The SARS-CoV-2 is a single-stranded RNA (ssRNA) virus that primarily affects the respiratory system resulting in a range of symptoms from fever, dry cough, loss of smell to life-threatening multi-organ failure. The

infection is also reported to result in various neurological manifestations such as stroke, encephalitis, olfactory-gustatory dysfunctions and GBS (Mao et al. 2020).

The link between SARS-CoV-2 and GBS was documented in a COVID-19-positive patient who presented acute weakness in legs, and since then, a number of case–control studies have been carried out (Luijten et al. 2021). The first case report from Kuwait documented the association of GBS with COVID-19 disease (Kamel et al. 2021). The study reported that a 72-year-old male developed acute progressive and ascending lower limbs weakness after 3 weeks of positive COVID-19 report (Kamel et al. 2021). Moreover, a systematic review involving the studies published during 1 January 2020 to 30 June 2020 found association of 42 GBS patients with SARS-CoV-2 infection (Uncini et al. 2020). The study suggested that GBS patients infected with SARS-CoV-2 infection exhibited the classical sensorimotor demyelinating GBS which responded to the usual treatments (Uncini et al. 2020). There was also a case report of two GBS patients associated with SARS-CoV-2 infection which showed neurologic improvement on IVIg (Bigaut et al. 2020). Additionally, a first reported case of GBS related to COVID-19 was found in the UK, wherein a 57-year-old man exhibited a progressive flaccid symmetrical motor and sensory neuropathy after 1 week history of cough and malaise. He was diagnosed with GBS secondary to COVID-19 (Webb et al. 2020). Moreover, in a recent review involving 95 studies published till December 2020 suggested that 220 patients had SARS-CoV-2-associated GBS (Finsterer and Scorza 2021). However, the study suggested that SARS-CoV-2-associated GBS is most likely to be secondary due to an immune reaction against SARS-CoV-2 since the virus has not been found in the CSF of any SARS-CoV-2-associated GBS patient (Finsterer and Scorza 2021).

Furthermore, the frequency of GBS with SARS-CoV-2 was higher (0.15%) as compared to patients without SARS-CoV-2 (0.02%) in Spain during COVID-19 peak (Fragiel et al. 2021). The infection is usually associated with demyelination present in AIDP form, although other forms have also been reported. The CSF parameter were similar between AIDP and SARS-CoV-2 associated GBS and patients also showed gadolinium enhancement of facial nerves or spinal nerve roots in MRI images (Bigaut et al. 2020). Molecular mimicry between SARS-CoV-2 and GBS-related proteins due to the presence of anti-GD1b, GM1, GM2, GD1a and GQ1b IgG antibodies can explain the pathogenesis; however, it still remains controversial. Interestingly, SARS-CoV-2 spike protein has been shown to bind to sialic acids present on gangliosides and can directly affect the neurons (Koike et al. 2021). These findings suggest a possible role of SARS-CoV-2 in GBS.

9.2.3 Protozoan Infections

The case reports of protozoan and parasitic infections associated with GBS are limited. The most common protozoan involved in manifestation of AIDP form of GBS is *Plasmodium falciparum* which is known to cause malaria in humans. It was first reported in 1992, where a 45-year-old patient was admitted after a history of fever, chills and headache due to malaria and later showed clinical symptoms of

GBS (Wijesundere 1992). Neurological examination was suggested for demyelination and presence of elevated protein in CSF, and it confirmed the GBS (Wijesundere 1992). Since then, a number of cases have been identified, and interestingly, in one patient there was a mixed infection of malaria and scrub typhus (Gangula et al. 2017). Another less virulent malarian protozoan, *Plasmodium vivax* was also found to be associated with AIDP (Kanjalkar et al. 1999; Berkowitz and Thakur 2014). Kala azar (Black fever) is caused by leishmania infection, resulting in chronic recurrent fever and in few instances has been associated with peripheral neuropathy (Llanos-Cuentas et al. 2013). GBS was linked with black fever for the first time in 1991, where a 22-year-old woman was admitted with motor weakness in limbs and dysphagia and had developed fever in the previous week (Fasanaro et al. 1991). Furthermore, a 15-year-old teenager with a history of leishmania infection was diagnosed with GBS (Ka et al. 2020). As for other protozoan, a rare case of an 8-year-old male patient infected with lung fluke was also diagnosed with GBS manifesting symptoms such as paralysis and pain in lower limbs (Yang et al. 2015). The immune response triggered by a protozoan infection may damage nerves by the release of pro-inflammatory cytokines (Yang et al. 2015), but the information available is rare because of low incidence. Furthermore, these pathogens can also result in dysregulation of gut–brain axis which can damage the peripheral nerves.

9.3 Vaccine-Induced Guillain–Barré Syndrome

In the previous section, we have described that there are several reported infections which increase the subsequent risk of GBS development. Additionally, besides that, GBS also develops after vaccination. The concern about any correlation between GBS and vaccine rose after the influenza vaccination season of 1976–1977. According to the reports, there was a significant upsurge in the number of GBS-positive patients within 6–8 weeks of getting the influenza vaccine (Schonberger et al. 1979). However, other subsequent studies did not report any positive correlation between the two. Additionally, a combined analysis from 1992–1993 and 1993–1994 vaccine campaigns in the USA also showed a marginal increase in GBS cases (Lasky et al. 1998). Furthermore, GBS has also been reported in individuals vaccinated with hepatitis and the meningococcal conjugate vaccine. However, here also the association was not that significant as incidences of GBS after immunization were the same as incidences with GBS only (Souayah et al. 2007).

Another vaccine that showed a relationship with GBS is the rabies vaccine. However, the risk was associated with rabies vaccines prepared from infected brain samples, apparently due to contamination with myelin antigens (Hemachudha et al. 1988). Extending further, surveys with oral polio vaccine and incidences of GBS did not show any increased positive correlation. Additionally, other vaccines such as measles, influenza, typhoid, cholera and diphtheria–tetanus–pertussis vaccines did not demonstrate any significant association between the occurrence of GBS (Haber et al. 2009). Lastly, in this section, it is also important to throw some

light on the association of GBS with the SARS-CoV-2 vaccine. Just in a period of 2 years i.e., from 2020 to 2022, there are numerous reports which describe the link between COVID-19 vaccine and GBS development. The majority of these findings including several case studies showed the development of neurological GBS-like symptoms upon vaccine administration (McKean and Chircop 2021). The possible explanation could be the elicited immune response which might trigger GBS-associated neurological difficulties. However, all of these reports even suggest that the risk of GBS upon covid vaccine is low, and it varies from one individual to other.

9.4 Role of Gut Microbiota in Guillain–Barré Syndrome

Altered gut microbiota or dysbiosis i.e., the depletion of a healthier gut microbiome, has been highlighted as one of the key pathological features implicated in the manifestation of various autoimmune and chronic inflammatory diseases. Various research findings have been trying to correlate the gut microbiome with the immune system (Maynard et al. 2012). Interestingly, both autoimmune and chronic inflammatory diseases have been characterized by tissue damage and functional deformities associated with the altered immune mechanisms (Rosenblum et al. 2015). It has been proposed that the healthier gut microbiota fluctuates the immune response, thereby triggering the production of cytokines, antibodies and antimicrobial peptides which aid in eliminating pathogens (Buffie and Pamer 2013). This highlights the importance of a mutual relationship between the host and its gut microbiota.

Interestingly, a considerable number of autoimmune diseases such as Guillain–Barré syndrome (Van den Berg et al. 2014a, b), Miller–Fisher syndrome (Koga et al. 2005) and Lyme arthritis (Nardelli et al. 2008) have been accompanied by infections with different pathogenic microorganisms, and hence it could be implied that these diseases could also have an altered gut microbiome. Infections with microorganisms like *Mycoplasma pneumonia*, HIV, *Campylobacter jejuni,* certain Herpesviridae and flu viruses have been reported as causative factors of GBS pathogenesis (Saxena 2016; Willison et al. 2016). They have been reported to cause an imbalance in the T_H1 cell population, resulting in the production of various cytokines contributing towards the disease progression (Saxena 2016). Interestingly, an increase in cytokines such as IL-17 and IL-22 has been found in the serum of GBS patients (Li et al. 2012). It has been proposed that infection of these pathogenic microorganisms could initiate cross-reactive antibody reactions, resulting in the production of autoimmune complexes which eventually leads to nerve damage (Yuki 2012). Therefore, all of these evidences imply a pivotal role of gut microbiota in influencing the progression of GBS. Supporting this, recent findings have also stated that transplanted human faecal microbiota enhances the GBS autoantibody responses in mice (Brooks et al. 2017). Taken together, all of these suggest an implacable role of the gut microbiome in the pathophysiology of GBS. Future

interventions which can alter the gut microbiome will aid in subjecting changes in disease-associated pathogenesis.

9.5 Management of Guillain–Barré Syndrome

9.5.1 Immunotherapy for Guillain–Barré Syndrome

As described earlier GBS is an acute immune-mediated disorder of the PNS. Different randomized controlled trails (RCTs) have stated that plasma exchange (PE) and intravenous immunoglobulin (IVIg) are the best available GBS immunotherapies till date. However, depending upon the individual genetic composition patients respond differently to the different immunotherapies. Some respond slowly, partially, and in some cases, it even worsens with either of the two (Liu et al. 2018). In view of this, other immunotherapies, for instance, corticosteroids had not been reported as quite efficacious in different clinical trials. Additionally, several other immunotherapies reported from different case studies or animal model studies could not effectively suppressed GBS in a large population and were only effective in some individual cases (Meyer zu Hörste et al. 2007). Therefore, it was extremely important to better understand the pathophysiology of GBS which will aid in the development of targeted molecular therapies for different available GBS variants. In the subsequent section, there is a detailed description of different available immunotherapies targeting the GBS.

9.5.1.1 Plasma Exchange

This treatment strategy focuses on the removal of immune triggering complexes such as circulating antibodies, complement complexes and cytokines from circulating plasma (Hartung et al. 1995; Lehmann and Hartung 2011) and replacing it with fresh frozen plasma or albumin from a healthy individual (Bouget et al. 1993). This treatment strategy was first utilized in 1959 on a patient suffering from thrombotic thrombocytopenic purpura, who got recovered after supplementing with fresh frozen plasma exchange, pointing towards the benefits of PE in suppressing autoimmune disorders (Rubinstein et al. 1959). After that in 1978, PE was again used to treat a patient with acute polyneuropathy who got immensely benefitted, suggesting the potential application of PE (Brettle et al. 1978). Considering this, PE was used as a treatment strategy against 245 GBS patients in an RCT and eventually then in a larger clinical trial (Liu et al. 2018). Thereafter, PE was considered a gold standard in the treatment of GBS, and it was established as the first validated therapy.

Considering about the range of patient-to-patient variability, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) had provided different administration guidelines for practicing PE on affected patients. The treatment is divided into two subclasses i.e., “Level A, Class II evidence” prescribed for non-ambulatory GBS patients, and another is “Level B, limited Class II” evidence prescribed for ambulatory patients (Hughes et al. 2003; Cortese

et al. 2011). Generally, five rounds of PE were advised over 1–2 weeks in GBS patients; however, it can vary depending upon the patient's severity (Hughes et al. 2003; Donofrio 2003). Interestingly, severe disease symptoms such as mechanical ventilation, difficulty with walking, and compromised muscle strength were effectively rescued within the course of PE treatment (Liu et al. 2018).

Besides all of the beneficial effects of PE on GBS, the former is also significantly associated with different adverse effects; for instance, thrombosis, pneumonia, hypocalcaemia, dilutional coagulopathy, hemodynamic instability, septicaemia and allergic reactions (Schröder et al. 2009). In addition to that, haemostatic disorders, defective cardiovascular status, increased rates of infections and pregnancy were also listed as other effective consequences of PE (Liu et al. 2018). Due to potential adverse effects and the lack of proper facilities required for PE, the broad-scale utilization of PE for GBS is limited. Additionally, prolonged monitoring and thereby the increased need for hospitalization along with alleviated medical costs lead to restricted usage of PE (Osterman et al. 1984; Espérou et al. 2000).

9.5.1.2 Intravenous Immunoglobulin

Another available immunotherapy for treating GBS is intravenous immunoglobulin (IVIg), which is derived from purified pooled immunoglobulins obtained from different blood donors. Initially, one of the earliest studies in 1988 demonstrated the usage of IVIg in severe GBS patients (Kleyweg et al. 1988). Subsequently, the first conducted RCT of IVIg in GBS also showed significant rescue proficiency similar to PE (Van der meché and Schmitz 1992). Likewise, as in PE, there are prescribed patterns of IVIg subjection and the outcomes of treatment vary depending upon individual genomic background and disease severity (Liu et al. 2018). For instance, patients exhibiting low serum IgGs were prescribed a higher dose or a second course of IVIg (Kuitwaard et al. 2009).

Similar to PE, IVIg does not show as many adversative effects as PE; generally, they are minor and rare occurring in less than 10% of patients (Liu et al. 2018). Some of the most severe reported pathological side effects associated with IVIg are headache, vomiting, renal failure, and myocardial infarction (Van der meché and Schmitz 1992; Hughes et al. 2003). Besides, PE and IVIg corticosteroids have also been utilized to treat this group of disorders. It was first time used in 1952 for treating GBS, and therefore for many years, it has been used as a treatment option. However, subsequent studies conducted after the 1970s had shown that corticosteroids were not that effective in treating GBS (Hughes et al. 2016).

9.5.1.3 Monoclonal Antibody

A humanized monoclonal antibody "Eculizumab" is currently under Phase II clinical trial for the treatment of GBS, and its results are awaited. Eculizumab targets the human complement molecule C5 which results in the inhibition of complement activation, pro-inflammatory C5a and membrane attack complex formation (C5b-9) (Yamaguchi et al. 2016; Davidson et al. 2017).

9.5.2 Role of Probiotics and Prebiotics in Guillain–Barré Syndrome

A peculiar role of the gut microbiome has been highlighted in governing the pathogenesis of GBS. The microbiome has been known to trigger an appropriate immune response to combat the pathogenic infectious agents. In view of this, probiotics and prebiotics could propose an effective, less invasive, economical and more acceptable treatment strategy in combating this disorder. Probiotics are the commercially available pool of microbiome that helps in aiding a healthier microbiome. On the other hand, prebiotics consists of complex carbohydrates and plant polysaccharides which act as a substrate for gut microbiota, thus aiding in establishing altered molecular pathway (Louis et al. 2016). Interestingly, researchers have noticed a beneficial effect of probiotics and prebiotics in combating several clinical conditions such as anxiety, stress, depression, inflammation and neurocognitive decline (Foster et al. 2021). Also, probiotics have also been widely utilized in combating several neurological deformities associated with neurodegenerative disease like Alzheimer's disease (Jiang et al. 2017).

As mentioned earlier, there is plenty of evidence that demonstrates changes in the population of Treg/T_H1 cells upon infection with different GBS causing pathogens (Steiner et al. 2010). Additionally, *C. jejuni*-mediated infections have been found to be alleviated upon treatment with probiotic strain *Lactobacillus helveticus* (Wine et al. 2009). Furthermore, different studies showed an increase in Treg cell population and in modifying T_H1/T_H2 ratio upon giving probiotic assistance (Kwon et al. 2010; Tanabe 2013). One study has demonstrated microbiota-altered host–pathogen interaction in a GBS mouse model, where they found increased colonization, T_H2 and autoimmune response in *C. jejuni* strain-dependent manner, suggesting that microbiota composition is a crucial factor for controlling susceptibility to GBS (Brooks et al. 2017). Recently, a study has explored the protective effects of *Bifidobacterium* on GBS animal models and monitored the IL-17A, IFN-γ, IL-4 levels and *Bifidobacterium* in patients with GBS (Shi et al. 2018). The study showed that plasma levels of IL-17A, IFN-γ and CSF IL-17A were significantly increased in the acute phase of GBS patients (Shi et al. 2018). Moreover, the plasma and CSF IL-17A levels were positively correlated with the GBS disability scale scores (GDSS), and the concentration of *Bifidobacterium* was negatively correlated with GDSS (Shi et al. 2018). Upon *Bifidobacterium* treatment, plasma IL-17A levels were significantly reduced in the Experimental Autoimmune Neuritis (EAN) animal model, and the study suggested that *Bifidobacterium* reduces GBS by regulating the function of T17 cells (Shi et al. 2018).

These studies suggest that probiotics may be useful for alleviating the symptoms of GBS; however, further animal studies and clinical trials for their role in GBS are needed.

9.6 Future Perspectives

Infection by *C. jejuni* still remains the predominant antecedent infection in GBS, and due to poor healthcare and unavailability of treatment, the cases are on rise in underdeveloped and developing countries. Therefore, care must be taken to reduce the

bacterial infections by improving sanitation, well-cooked poultry products and public awareness about the mode of transmission. Other bacterial species, viruses and protozoans have also been associated with GBS development (Table 9.1), and prevention of these infections can be an effective strategy to combat GBS. Advancement in epidemiology, immunology and microbiology has helped improved our understanding in pathophysiology of GBS. Molecular mimicry between epitopes on pathogens and neural proteins resulting in immunologic damage to peripheral nerves is the most plausible explanation for GBS pathogenesis (Fig. 9.1); however, it does not explain all known cases and hence suggesting for the involvement of newer pathogenic mechanisms. Furthermore, the microbiota–neuronal–immune triangle can explain the missing link between nervous system and immune system which is involved in GBS; however, this needs to be extensively evaluated in future in animal models.

With the emergence of new variants of SARS-CoV-2 and development of global commerce and travel, infectious diseases are a consistent public health threat. The infection often results in the manifestation of GBS, but the numbers are limited, and therefore, a large-scale case–control study along with a predefined case definition for diagnosis of GBS and follow-up with uniformity in electrodiagnostic criteria is greatly needed to establish a true link between GBS and SARS-CoV-2. Currently, there is no cure for GBS, and plasma exchange and intravenous immunoglobulin have been shown to be more effective than supportive treatment alone in recovery of patients, but these are expensive. Despite the positive effects associated with already available immunotherapy, there are few instances where they fail and therefore in future, therapy trials should take into account the age of the patient, severity of symptoms, and other factors. They also should consider evaluating the genetics of both the host and pathogen to reveal risk or protective factors at population level. Lastly, with the possible involvement of gut–brain axis in GBS pathogenesis, probiotics-mediated induction of Treg, and probiotics-based modulation of T_H1 (and T_H17)/T_H2 balance; implementation of probiotics and prebiotics can aid in providing a better, non-invasive, economical treatment strategy for GBS.

9.7 Conclusions

This chapter provides systematic and precise information on the role of microorganisms involved in GBS pathogenesis and management by traditional immunotherapy and state-of-the-art probiotics and prebiotics. GBS is an autoimmune disorder that typically develops within 4 weeks following infection with various pathogens. Past decade has shown increased incidence of GBS due to outbreaks of Zika virus and SARS-CoV-2, though the association with latter is still controversial. Vaccination has also been found to be linked to GBS though such cases are limited. This still raises the question of overall risk–benefit ratio of vaccines in prevention of diseases like COVID-19. Despite limited knowledge on composition of gut microbiome in healthy and GBS-affected patients and the underlying possible pathogenic mechanism, it has exciting implications for

understanding the unknown aetiology of GBS and possible development of microbiome-targeted therapies.

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Microorganisms in Pathogenesis and Management of Neuromyelitis Optica Spectrum Disorder

10

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease of the central nervous system with astrocytopathy characteristics. Antibodies against aquaporin-4 water channels which are mainly located in astrocyte podocytes play an important role in NMOSD pathogenesis. Like other autoimmune disorders, it seems that both genetic and environmental factors are involved in NMOSD risk, but the role of environmental risk factors is more significant. Infections are known to be an effective factor not only in the incidence but also in the exacerbation of autoimmune diseases. In this chapter, the roles of microorganisms in two categories of viruses and bacteria in the pathogenesis and management of NMOSD patients are discussed. In this regard the relation between infection with tuberculosis, *Helicobacter pylori*, Epstein–Barr virus, SARS-CoV-2, varicella-zoster virus, dengue virus, cytomegalovirus, herpes simplex virus 2 and Zika virus, as well as gut microbiome and NMOSD occurrence are mentioned. On the other hand, susceptibility of NMOSD patients for developing infectious diseases due to receiving immunosuppressive drugs and the role of infection in NMOSD attack and disease exacerbation are outlined.

Keywords

Neuromyelitis optica spectrum disorder · Environmental risk factors · Microorganisms · Viruses · Bacteria · Infection · Gut microbiome

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10.1 Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS), which mainly involves the optic nerve and spinal cord, so it can consequently cause many disabilities (Wingerchuk et al. 2015). The prevalence of this disease varies from 0.51 to 4.4 per 100 thousand people (Eskandarieh et al. 2017b). As well, in this disease, the ratio of women to men is 3:1 to 9:1, and the average age of prevalence is 20–40 years (Sahraian et al. 2017), which is higher than that of multiple sclerosis (MS), as a similar disease (Eskandarieh et al. 2017a). Our knowledge of this disease is increasing progressively. The disease was once considered as a part of MS disease. The similarity of the symptoms, especially blurred vision and paresis, which are common in both of these diseases, added to this suspicion. However, it became gradually clear that these two diseases are two separate diseases with separate pathogenesis and different factors involved in them. Recognition of NMOSD entered into a new phase, especially in 2005 (Lennon et al. 2005) with the discovery of the aquaporin 4 antibody. Since then, it has been established that NMOSD is an autoimmune disease in which specific antibodies, which are responsible for many manifestations of the disease, can cause the disease (Wu et al. 2019). Moreover, it was found that the disease, unlike MS that is a demyelinating disease, is an astrocytopathy, and the antibody is more prone to attack the water channels located in the astrocyte podocytes (Wu et al. 2019). Therefore, the more the water channel, the more likely to be involved with this disease. Accordingly, this explains many of the symptoms of this disease. With the discovery of aquaporin 4 antibody, it was revealed that the disease is more of a spectrum than a specific disease, and we can also observe different forms of involvement in this disease (Wingerchuk et al. 2015). Apart from the spinal cord and optic nerve, which are known as the most involved areas in this disease, other areas of the central nervous system such as the diencephalon, area postrema, and the hemispheres can also be involved in this disease (Wang et al. 2018). Additionally, it has been shown that this disease can involve some areas outside the central nervous system such as the middle ear, myocardium, and placenta (Lennon et al. 2005). Of note, the next issue that can complicate the form of the disease is its association with other autoimmune diseases. This disease was found to be associated with a wide range of autoimmune diseases such as myasthenia gravis, lupus, and Sjögren's, so this leads its manifestations to become more diverse (Shahmohammadi et al. 2019). Although a significant proportion of patients with this disease are seropositive, and antibodies can also be detected in them, about 23% of these patients are seronegative who are clinically and radiologically different from seropositive cases (Wingerchuk et al. 2015). It has been found that the disease in these patients is less severe and only associated with a lower degree of disability (Dauby et al. 2021). However, in recent years, it has been found that some seronegative patients are resulted as positive for antibodies against myelin oligodendrocyte glycoprotein (MOG) that form a separate and different group (Ojha et al. 2020). Therefore, there is a possibility that other unknown antibodies may also be resulted as positive in seronegative patients who are negative for anti-MOG; accordingly, this requires further studies.

10.2 Pathogenesis

As mentioned earlier, NMOSD is an astrocytopathy, and antibodies against water channels were observed to play a very important role in the pathogenesis of this disease (Papadopoulos and Verkman 2012). This antibody is an IgG1 that binds to water channels, which are mainly located in astrocyte podocytes, and consequently causes the process of astrocytopathy and some subsequent clinical manifestations (Ikeshima-Kataoka 2016). Although antibodies play key roles in the development of the disease and its pathogenesis, this is a very complex process and involves several stages, each one of which is considered the basis for creating new drugs. Complement-mediated astrocyte damage occurs after the antibody binding to these water channels. Subsequently, it leads to granulocyte infiltration, oligodendrocyte death, and finally neuronal death (Duhan et al. 2009). This antibody is also involved in IgG/IgM deposition (Roemer et al. 2007). Apart from all the above-mentioned consequences, other elements and cells are also involved in the pathogenesis of the disease. It is currently known that mast cells are also involved in the pathogenesis of this disease. Correspondingly, these can be involved in the pathogenesis of this disease as innate and adaptive immune response regulators (Kim et al. 2019). The roles of Th17, Th2, and their cytokines have been widely discussed in the pathogenesis of this disease. These cytokines, which include IL-6, IL-1β, IL-17, IL-21, IL-22, IL-23, and TGF-β, along with the cells, can play a direct role in the pathogenesis of the disease. Moreover, they can cause brain damage by stimulating B cells as well as inducing antibody production by these cells (Zhang et al. 2018; Uzawa et al. 2014; Lin et al. 2016). It was found that the levels of these cytokines in both serum and cerebrospinal fluid samples of these patients are significantly higher than those of healthy individuals, showing their direct role in causing disease (Lin et al. 2016). This also indicates the complexity of the pathogenesis of this disease. Since the attacks of this disease can be debilitating and even fatal, the recognition of the risk factors and the factors involved in causing the disease or in causing the attacks can play an important role in preventing the disability resulted from that. In this chapter, we firstly took a brief look at the risk factors related to this disease and then focused on the roles of microorganisms in causing the disease and in attacks, and how to treat the disease.

10.3 Risk Factors

Similar to many other diseases of the immune system, the risk factors for this disease are divided into two general categories as follows: environmental and genetic (Naser Moghadasi 2020). It seems that the role of genetic factors in a person developing NMOSD is less than their role in patients with MS (Naser Moghadasi 2020). One study found that having a family history of MS, unlike NMOSD, can be considered as a risk factor (Eskandarieh et al. 2017a). While the rate of familial MS is reported to be 13% (Salehi et al. 2020), which appears to be increasing (Eskandarieh et al. 2018a), in a small number of studies conducted on familial NMOSD, this rate has

been reported to be 3% (Matiello et al. 2010). However, several cases of familial NMOSD have been reported in this regard. Additionally, those studies on the genetic risk factors indicated the role of various genes such as HLA-DRB1 alleles and luster of differentiation 58 (CD58) polymorphism in the development of the disease (Matsushita et al. 2020; Kim et al. 2014). As mentioned earlier, the role of environmental factors in the development of NMOSD was found to be more significant. Nevertheless, limited studies have been done in this field. In the study by Eskandarieh et al., some factors such as low sea food intake and low dairy consumption have been reported as the risk factors for NMOSD (Eskandarieh et al. 2018b). In some other studies, high fat intake and little consumption of grains and vegetables have been reported as nutritional factors that can increase the risk of NMOSD (Rezaeimanesh et al. 2021, 2020). Infections have always been considered as a predisposing factor in all autoimmune diseases. Moreover, they are not only involved in causing these diseases, but can also exacerbate them. As well, numerous microorganisms such as *Mycobacterium tuberculosis*, *Helicobacter pylori*, and varicella zoster virus have been implicated in causing these diseases. At the beginning of the COVID-19 pandemic, the possibility of the virus involvement in the development of NMOSD as well as the intensification of its attacks has been raised. In the following, the roles of microorganisms in the pathogenesis and management of patients with NMOSD are discussed.

10.4 The Role of Microorganisms in the Pathogenesis of Neuromyelitis Optica

10.4.1 Bacteria

10.4.1.1 *Mycobacterium tuberculosis*

Numerous studies have been conducted on the relationship between tuberculosis (caused by *M. tuberculosis)* and NMOSD, either as a case report or as a cross-sectional study. However, the relationship between these two diseases is controversial yet. In this regard, some case reports stated different conditions for the relationship between the two diseases. In some cases, it was found that NMOSD occurs after or during tuberculosis. Grieve et al. in their study reported a 48-year-old patient who developed blurred vision and sensory disturbances during treatment for tuberculosis; therefore, the patient was diagnosed with NMOSD after performing a thorough examination (Grieve et al. 2020).

In another case reported by de Saráchaga et al., a 34-year-old woman presenting weakness and progressive numbness of the limbs followed by dysarthria was diagnosed with NMOSD. However, during her treatment, she suffered from respiratory distress and pleural effusion, and with further examinations, tuberculosis was diagnosed (de Saráchaga et al. 2020). In this case, unlike the previous case, tuberculosis was diagnosed after NMOSD. In a similar report, Bhatty et al. described a young girl who was referred because of paraplegia and treated with the diagnosis of

NMOSD. However, during her treatment, she developed ascites and was eventually diagnosed with abdominal tuberculosis (Bhatty et al. 2015).

Besides the above-mentioned case reports, two other studies have also been published on the association between NMOSD and tuberculosis, which gave contradictory answers to the possibility of an association between these two diseases. The study by Zatjirua V et al. in 2011 examined 14 patients with NMOSD, of whom 11 cases had tuberculosis either before or at the time of the diagnosis of NMOSD. The average time of developing TB to NMOSD was estimated as 4 weeks. The authors concluded that these data suggest an association between tuberculosis and NMOSD, which may possibly be due to the role of the mediated immune mechanism (Zatjirua et al. 2011). However, in the Li et al.'s study published in 2014, this association was not confirmed. Correspondingly, they found no significant difference in terms of tuberculosis between patients with NMOSD and the control subjects (Li et al. 2014). It is possible that these accompaniments may be random (Zayet et al. 2021); therefore, further investigations are required in this regard. Based on the available data, it is not possible yet to provide a definitive theory on the role of *Mycobacterium tuberculosis* in the pathogenesis of this disease.

10.4.1.2 Gut Microbiome

The role of the intestinal microbiome in the development of autoimmune diseases is increasingly considered, and NMOSD is no exception in this regard. Several studies have previously shown that the intestinal microbiome of these patients is different from those of MS patients and healthy individuals, in terms of both the content and percentage of available strains.

Shi et al. published a paper in 2020 to compare the intestinal microbiome of people with NMOSD with that of healthy people. Accordingly, they found that the rate of pathogenic strains (*Flavonifractor* and *Streptococcus*) was higher in people with NMOSD than that of healthy people. Additionally, the strains of *Faecalibacterium*, *Lachnospiracea_incertae_sedis*, *Prevotella, Blautia, Roseburia, Romboutsia, Coprococcus*, and *Fusicatenibacter* were observed to be less than the microbiome of healthy individuals (Shi et al. 2020). As well, it has been found that the characteristics of the intestinal microbiome are different among seropositive and seronegative patients (Zhang et al. 2020).

In a study conducted by Cree et al. on 16 NMOSD patients and 16 healthy individuals, it was found that the type of intestinal microbiome in the patients was completely different from that of the healthy individuals, especially the amount of *Clostridium perfringens* in the intestines of these patients, which was significantly overrepresented (Cree et al. 2016). *Clostridium perfringens*, which are located in the intestines of these patients, can play a role in regulating the balance between the regulatory T cells and Th17 cells; thus, these can be involved in the pathogenesis of these patients (Zamvil et al. 2018). In another study by Pandit L et al., it was found that the amount of *Clostridium bolteae* was significantly higher in seropositive patients compared to seronegative patients; however, the microorganism was not observed in their studied healthy individuals. This microorganism has been found to contain aquaporin-related proteins bearing a striking sequence similarity to

aquaporin-4 peptides. So, this highlighted its role in stimulating T cells as well as its participation in the pathogenesis of the disease (Pandit et al. 2021).

Due to the above-mentioned reasons and the roles of intestinal microbiome in the development and pathogenesis of other autoimmune diseases, a microbiota intervention can be considered as the treatment for these patients. It was indicated that the regulation of the intestinal microbiome can repair the intestinal mucosal barrier and also modulate intestinal immunity and peripheral immunity (Cui et al. 2020). Consequently, this fact opens up new therapeutic horizons for scientists in this field.

10.4.1.3 *Helicobacter pylori*

Due to the high prevalence of *Helicobacter pylori* in the community, this microbe has always been considered as a stimulant of the immune system, and consequently, it was shown that it is involved in the development of autoimmune diseases. Accordingly, some studies have also been published on its possible role in the development of NMOSD. Li et al. in their study examined the immune response to *Helicobacter pylori* neutrophil-activating protein in patients with MS and NMOSD, as well as normal individuals. As a result, it was found that *Helicobacter pylori* seropositivity was higher in patients with NMOSD. Moreover, this was true for anti-*Helicobacter pylori* neutrophil-activating protein antibody, and in this regard, the interesting point is that the titer of this antibody is directly related to the degree of disability (Li et al. 2009).

Furthermore, Yoshimura et al. found that a history of *Helicobacter pylori* infection is a risk factor for NMOSD seropositive cases (Yoshimura et al. 2013). The same result was also confirmed in another study performed by Long et al. (2013).

Although these studies are limited, however, these studies indicated the role of *Helicobacter pylori* in the development of neuromyelitis optica. It may also be involved in the development of disability in people with this disease. Nevertheless, whether the early treatment of *Helicobacter pylori* can reduce the risk of developing NMOSD still is a question that should be considered to be answered in future studies.

10.4.2 Viruses

10.4.2.1 Epstein–Barr Virus (EBV)

Given the prominent role of EBV in the pathogenesis of MS (Bar-Or et al. 2020), so it is reasonable to consider its possible role in NMOSD as well. However, the role of this virus seems to be different in these two diseases. Correspondingly, the obtained results are completely contradictory, which can be related to the small sample size in all studies. In another study, Simon et al. found no association between anti-Epstein–Barr nuclear antigen (anti-EBNA) titers and NMOSD (Simon et al. 2015). In addition, Graves et al. came to the same conclusion in examining the environmental risk factors for NMOSD (Graves et al. 2014).

On the other hand, Masuda et al. in their research reported a different conclusion. They found that the serum level of anti-early antigen IgG antibodies in NMOSD

patients was significantly higher than those of MS patients and healthy individuals, indicating the active EBV replication in these patients (Masuda et al. 2015). Moreover, Mori found that although a history of EBV is associated with a higher risk of developing MS, with regard to NMOSD, it is the re-activation of EBV that exacerbates the risk of NMOSD in patients in the future (Mori 2015). However, more studies are required to confirm this finding.

10.4.2.2 SARS-CoV-2

Soon after the start of the COVID-19 pandemic in December 2019, scientists realized that the extent of the infection with this virus goes far beyond a contagious deadly infection manifesting itself with lung involvement. As well, from the very beginning, it was realized that the virus could not only directly infect the brain (Montalvan et al. 2020); however, it is an immunogenic virus that could cause various autoimmune diseases (Montalvan et al. 2020; Naser Moghadasi 2021). Immediately after the start of the pandemic, numerous reports of various autoimmune diseases, including autoimmune diseases related to the brain, were published (Montalvan et al. 2020). Of note, NMOSD was no exception in this regard. Additionally, there have been some reports of NMOSD during or after COVID-19, showing new angles of the relationship between the coronavirus and NMOSD.

Ghosh et al. reported a 20-year-old man who experienced nausea, vomiting, and hiccups, as well as manifesting progressive limb weakness by passing 10 days from developing COVID-19, who was finally diagnosed with NMOSD and treated with methylprednisolone and rituximab (Ghosh et al. 2020). Ruijter et al. also reported a 15-year-old man presenting with blurred vision in both eyes by passing a few weeks from developing COVID-19. Finally, he was diagnosed with NMOSD and then treated with methylprednisolone (de Ruijter et al. 2020). On the other hand, Batum et al. reported a 50-year-old woman presented with fever, malaise, cough, and lower extremity weakness and after performing necessary examinations, she was diagnosed with co-infection of COVID-19 and NMOSD (Batum et al. 2020). Shaw et al. also reported a man who developed blurred vision, lower limb weakness, and sphincter disorder by passing 9 days from developing COVID-19. Unfortunately, the patient died due to the exacerbation of COVID-19, but his anti-aquaporin 4 antibody test resulted as positive (Shaw et al. 2020).

As indicated, the association between COVID-19 and NMOSD can occur at any age and in both sexes with any clinical pattern. So, this shows the possible role of Coronavirus in the pathogenesis of this disease. In fact, this is an issue that is not limited to the age and gender of the affected individuals. Due to the current COVID-19 pandemic, we should probably expect more cases of NMOSD.

10.4.2.3 Varicella Zoster Virus (VZV)

There is an increasing trend toward the reports of the role of this virus in the pathogenesis of NMOSD, and it seems that we need more extensive and comprehensive studies in order to better understand the role of this virus in the pathogenesis of the disease. In 2009, Heerlein K et al. in their study reported a 63-year-old woman diagnosed with shingles in her lumbar area. By passing 2 weeks from developing

shingles, the patient was presented with weakness and numbness in his left leg, and on magnetic resonance imaging (MRI), longitudinal extensive transverse myelitis (LETM) was seen in both the cervical and thoracic spinal cords. The anti-aquaporin 4 antibody test was positive; therefore, the patient was diagnosed with NMOSD and then treated with corticosteroid (Heerlein et al. 2009).

In another study, Park et al. reported a young woman who developed LETM following herpes zoster and was under the treatment for herpes-related LETM. However, with the recurrence of myelitis and positive anti-aquaporin 4 antibody, she was treated with a diagnosis of parainfectious NMOSD (Park et al. 2013). Machado et al. also reported a 77-year-old woman who was hospitalized with shingles; however, she quickly developed paraparesis, urinary incontinence, and sensory problems. Moreover, LETM was seen on thoracic MRI. Six months later, the patient developed chorea symptoms. As well, brain MRI showed periependymal involvement of the fourth ventricle. Due to the fact that this feature is mostly observed in NMOSD, so the patient was checked for anti-aquaporin 4 antibody at this stage, which resulted as positive, and subsequently the patient was treated with azathioprine and prednisolone with a diagnosis of NMOSD (Machado et al. 2015).

Furthermore, Suda et al. reported a 53-year-old man who developed myelitis 7 days after varicella zoster. While the patient was diagnosed with zoster-induced myelitis, his test was positive for anti-aquaporin 4 antibody (Suda et al. 2017). In reviewing the previously performed case reports, it is important to note that the clinical manifestations of both varicella zoster and NMOSD are quite diverse in both sexes and at different ages of involvement. Matsumoto et al. in their study reported a 26-year-old woman who developed both NMOSD and extensive zoster during pregnancy, and her situation was improved with intravenous immunoglobulin (IVIG) injection (Matsumoto et al. 2018). Eguchi et al. reported a 55-year-old woman who was concurrently suffering from NMOSD and VZV radiculomyelitis (Eguchi et al. 2020). Finally, in 2020, Turco et al. reported the first child case who had VZV infection along with NMOSD (Turco et al. 2020).

As stated earlier, reports on the co-occurrence of VZV infection and NMOSD are increasing. However, all the reported cases were in the case reports, and a comprehensive study has not been done on antibody levels against zoster virus in these patients and its comparison with healthy individuals yet. Correspondingly, such a study could determine the possible role of varicella zoster virus in NMOSD.

10.4.2.4 Dengue Virus

It was indicated that dengue virus can lead to fever, headache, myalgia, and skin lesions, and in less common cases, to bleeding and death (Muller et al. 2017). As well, there have been reports of dengue fever associated with NMOSD. In 2007, an 11-year-old Japanese girl living in northern Brazil was reported with the developed NMOSD along with blurred vision and myelitis after a week of suffering from dengue fever. Eventually, she was treated with corticosteroids and then recovered. Notably, dengue fever is confirmed by IgM testing against the virus in cerebrospinal fluid (de Sousa et al. 2006). Puccioni-Sohler et al. also reported a 17-year-old girl who developed both NMOSD and dengue fever concurrently. Although the antibody

was negative in this patient, the combination of clinical symptoms and MRI findings finally confirmed the diagnosis of NMOSD (Puccioni-Sohler et al. 2017).

All the above-mentioned cases were seronegative in terms of antibodies against aquaporin 4. However, in 2018, Lana-Peixoto et al. in their study reported two patients who had NMOSD concurrent with dengue fever. Accordingly, one of the patients was presented with optic blurred vision and an initial diagnosis of optic neuritis and the other one presented brainstem symptoms, but unlike the previous cases, both patients resulted as positive for anti-aquaporin 4 antibody (Lana-Peixoto et al. 2018).

10.4.2.5 Cytomegalovirus (CMV)

Similar to other viruses, the occurrence of NMOSD has been reported after infection with CMV. In 2007, Tran et al. reported a 34-year-old patient who developed myelopathy and blurred vision after being infected by CMV, and was then diagnosed with NMOSD (Tran et al. 2007).

Luo et al. also reported a 40-year-old woman who was diagnosed with NMOSD and then treated with methylprednisolone and IVIG, followed by plasmapheresis. However, no improvement was observed. Therefore, she was referred to another center to receive a better treatment. On the third day of hospitalization, the patient developed hematochezia, which was eventually diagnosed as CMV infection using a biopsy; therefore, she was treated with ganciclovir. Following the CMV treatment, the patient's condition in terms of limb weakness and blurred vision was improved. Moreover, the authors concluded that the patient's symptoms did not improve due to an infection that might itself play a role in the development of NMOSD, since the treatment of the infection consequently led to the improvement of NMOSD condition (Luo et al. 2020). In cases with the occurrence of NMOSD after the development of an infection, whether the treatment of that infection would improve the NMOSD condition or not, they should be considered in further studies.

10.4.2.6 Herpes Simplex Virus 2 (HSV2)

The role of herpes in many autoimmune diseases like MS has been previously discussed in many studies done in this regard (Ishaq et al. 2015). However, there have been few reports of the association between this virus and NMOSD. Marin Collazo et al. reported a 66-year-old man referred to the hospital with lower extremity weakness, paresthesia, and urinary problems. This patient had a history of recurrent genital infections with the herpes virus from 40 years ago. Although he did not have a herpes infection at the time of admission, an examination of the cerebrospinal fluid using polymerase chain reaction (PCR) method revealed HSV-2 DNA, which confirmed the HSV infection of the central nervous system. Anti-aquaporin 4 antibody also was positive in further studies, which indicated the simultaneous presence of two diseases of central nervous system infection, as herpes and NMOSD, in this patient. Therefore, the patient was treated simultaneously with both methylprednisolone and acyclovir (Collazo et al. 2018).

As mentioned earlier, despite the prominent role of this virus in various autoimmune diseases, there have been few reports on its association with NMOSD. In this

regard, Etemadifar et al. in 2019 studied the level of antibodies against HSV in the serum of patients with MS and NMOSD, as well healthy individuals; however, they found no significant differences among them (Etemadifar et al. 2019).

10.4.2.7 Zika

In 2019, MC et al. reported a 35-year-old Brazilian man presented with fever, myalgia, and arthralgia. Four days later, he reported suffering from urinary retention with paraparesis. In addition, brain MRI was normal, but hyperactive lesions were observed in cervical and thoracic MRI. Due to the infectious symptoms and endemicity of Zika in the area, this patient was examined for other infectious diseases, and Zika PCR was positive in cerebrospinal fluid. As well, methylprednisolone was started for the patient, but the patient's symptoms did not improve, and he then reported constipation, vomiting, and hearing loss. On re-MRI, the lesions of the central nervous system increased, and this time, a lesion was also observed in the pons.

Therefore, despite the negative result of anti-aquaporin 4 antibody, the patient was diagnosed with NMOSD. Afterward, although he was treated with IVIG, he developed blurred vision with pain in the right eye, and according to the MRI in which optic nerve involvement was evident, he was then treated with methylprednisolone and finally recovered. So, the authors concluded that in cases where the diagnosis of NMOSD is made in an area where Zika infection is endemic, it is better to consider it as a factor involved in the pathogenesis of the disease (Aspahan et al. 2019).

10.5 Diagnostic of NMOSD

Infections can be considered in several ways when diagnosing NMOSD. Firstly, many infections can mimic the symptoms of NMOSD in various ways, including some diseases such as human immunodeficiency viruses (HIV) (Brew and Garber 2018), syphilis (Kabanovski et al. 2021), or Lyme (Summer and Rupprecht 2019). Consequently, it was shown that these diseases can cause some symptoms such as myelopathy or blurred vision; therefore, they can be considered as differential diagnoses of NMOSD. Due to newly appeared viral diseases such as COVID-19, it is very important to pay more attention to these differential diagnoses. Currently, we know that COVID-19 could be associated with the central nervous system involvement (Montalvan et al. 2020), as well; some reports were published on myelitis following COVID-19 (Chakraborty et al. 2020) and subsequent optic neuritis (Tisdale and Chwalisz 2020). These cases are also among the main symptoms of NMOSD.

On the other hand, a number of the microorganisms discussed earlier can lead to the presentation of some symptoms such as myelitis in their involvement. Since these microorganisms are also involved in the development of NMOSD disease, so in these cases, it is better to check for NMOSD and not attribute everything to the complications resulted from the microorganism itself as an infectious agent.

The next issue, as was discussed, was the association between numbers of infections with NMOSD itself, which are important to be considered in several ways. The first point is that later or no diagnosis of infections can be dangerous for the patient, as the treatments used in NMOSD are immunosuppressive therapies. Accordingly, these therapies, if co-infected with an infectious disease, can exacerbate the associated infectious disease and even be fatal to the patient.

As the second point, as seen in the association of NMOSD and CMV (Luo et al. 2020), failure to treat infections can consequently lead to NMOSD treatment failure. Therefore, it is very important to pay more attention to possible concomitant infectious diseases, especially in areas that are considered as endemic in terms of a particular infectious disease.

10.6 The Role of Infections in Causing an Attack in Patients with NMOSD

Attacks play an extremely important role in NMOSD, because they can cause severe kinds of disability in patients. Therefore, it is important to pay attention to the factors predisposing NMOSD patients to attacks and then to prevent them. Infections in autoimmune diseases have always been considered as causative agents of the relapses. As well, the same is true for NMOSD. Therefore, the prevention of infectious diseases can be effective on preventing disability in these patients (He et al. 2019; Saab et al. 2016). On the other hand, any infection in these patients should be considered and treated. This can reduce the risk of attacks in these patients.

10.7 Infection of NMOSD Patients with Infectious Diseases and Its Complications

It was indicated that NMOSD patients are prone to side effects due to taking immunosuppressive drugs, especially the increased risk of developing various infectious diseases. Several reports have been published on the complications of these infectious. Pneumonia and urinary tract infections are known as the side effects of rituximab (Moghadasi et al. 2019; Damato et al. 2016). Cases of death following infection have also been reported in patients consuming this drug (Kim et al. 2015).

Studies on the risk and morbidity of patients with NMOSD who developed COVID-19 have shown higher rates of hospitalization (Sahraian et al. 2020) and mortality in them who were mainly rituximab users (Esmaeili et al. 2021). So, these have made the treatment of these patients a challenge for neurologists as the situation can happen with any other infectious disease.

10.8 Management of NMOSD Through Microorganisms

It has not yet been established whether probiotic, prebiotic, and synbiotic supplementation can alleviate NMOSD symptoms or not. But, there are growing evidences on the beneficial role of using them in the management of MS. An altered gut microbiota is reported in MS patients compared with healthy population. RCT designed studies showed the effect of intervention by probiotics in improvement of mood, disability, quality of life (depression, anxiety, stress, general health and fatigue), metabolic and clinical markers vs. placebo group in MS patients (Kouchaki et al. 2017; Blais et al. 2021). A human study outlined induction in anti-inflammatory peripheral immune response by probiotics administration (Tankou et al. 2018). In another study experimental autoimmune encephalomyelitis (EAE) was suppressed using a mixture of five probiotics, due to inducing regulatory T cells and reducing T helper 1 and 17 polarization (Evans et al. 2018; Kwon et al. 2013).

It seems that dietary intake could be effective in the alternation of microflora. So that western diet could lead to dysbiosis while physical activity, higher intake of fruits, vegetables, legumes, fish, prebiotics, and probiotics cause restoration or maintenance of a healthy symbiotic gut microbiota (Riccio and Rossano 2015). Riccio et al. in 2015 suggested consumption of probiotics such as *Bifidobacterium lactis, Clostridium butyricum*, and *Lactococcus lactis* and prebiotics including oligofructose, inulin, bran, and lactosucrose in MS patients. They also highly recommended the combination of prebiotics and probiotics in these patients (Riccio and Rossano 2015).

Based on our knowledge, there are no human study on commensal therapy in NMOSD or MS. But some studies investigated the role of commensal therapy in animal models of MS (Blais et al. 2021). Commensal therapies resulted in delay in EAE onset and reduction in incidence, clinical scores, demyelination, and inflammatory CNS infiltration (Blais et al. 2021).

Due to evidences on beneficial effects of probiotics or commensal therapies in MS patients, it could be concluded that these complementary therapies may be helpful for NMOSD patients, too. But investigation in this area is needed to prove this hypothesis.

10.9 Conclusion

Although the risk factors for NMOSD have not been studied extensively, some evidences suggested that infections play an important role in the pathogenesis of the disease. Infections can also be regarded as an effective factor on facilitating attacks of this disease. On the other hand, due to the use of immunosuppressive drugs, the risk of infection in these patients is high, which can even increase the risk of death. Therefore, it is very important to pay attention to the roles of microorganisms in the development and course of the disease.

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Microorganisms in Pathogenesis and Management of Acute Disseminated Encephalomyelitis (ADEM)

11

Amit Agrawal and Sayan Bhattacharyya

Abstract

Autoimmune diseases are said to occur when the immune system of the host reacts against its own antigens, also called self-antigens. Many microorganisms trigger and initiate autoimmunity by a number of mechanisms like bystander lysis and antigenic mimicry. Autoimmunity can also be flared up by a wide variety of microbes. Acute disseminated encephalomyelitis (or ADEM) is one such autoimmune disease in which either microbes or immunizations have an important role to play. ADEM is an acute, rapidly progressive autoimmune disorder. It is characterized by demyelination in the white matter and deep gray matter of the brain and spinal cord that takes place due to inflammation occurring in response to a preceding infection or even cases of immunization. Many underlying mechanisms can ultimately lead to the occurrence of ADEM following any infection or vaccination, such as molecular mimicry, nonspecific sensitization by the body's own reactive T-cells, axonal injury, and edema. As no specific etiologic agent has been constantly identified behind ADEM, and the role of any specific underlying mechanism is still debated, more research is needed to further establish the relationship with these mechanisms. If microbial etiologies and the link behind these autoimmune diseases are more and more deliberated upon, new strategies can be formulated to target these microbes flaring up autoimmunity. A complex interplay of factors like the host genotype, host microbiome, the environment, diet, and microbial etiology can help in developing so many autoimmune diseases. These things are indeed very interesting to note and study. Here,

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we thus try to present relevant information about the epidemiology and pathogenesis behind the microbes causing autoimmunity in general and ADEM in particular.

Keywords

Autoimmune · Infection · Vaccination · Microorganisms · Acute disseminated encephalomyelitis (ADEM) · Immune response · Demyelination · Microbes · Encephalomyelitis · Bacteria · Viruses

11.1 Introduction

Microbes, including bacteria and viruses, play a definitive role in inducing autoimmunity. Pathogenic and commensal microorganisms trigger the production of autoantibodies and bind themselves to the brain. They then influence the behavior in the susceptible hosts (Hornig 2013). Nowadays, this is indeed a very interesting and hot research topic. Normally commensals help in regulating this autoimmunity; any disruption of the normal microbiome may trigger autoimmunity. Nonpathogenic microorganisms which are present in various niches of the animal or human body are called commensal microbiota, and there are three major characteristics of these host–commensal interactions. Mechanisms of central tolerance or deletion and inactivation of the self-reactive lymphocytes and their active inhibition by the regulatory T cells (Tregs) are there to minimize autoimmunity. However, potentially autoreactive immune cells are always on guard in the hosts (Chervonsky 2013).

Autoimmune diseases can be broadly divided into two major groups: Group I consists of diseases that require the innate–adaptive immunity connection for their beginning, and Group II comprises those diseases for which this connection is unimportant. Group II diseases are mostly monogenic disorders that occur due to the loss of control over one of the major mechanisms which control adaptive immunity, like negative selection or generation of the Tregs (Esposito et al. 2015).

In experimental animals, commensal microbial flora or conventional microbiota is known to induce many diseases. However, they can also harbor pathobionts or microbes that do not normally cause any pathology in the normal scenario. Thus, they are not part of this specific list of pathogens. This category of commensal microorganisms can be a worthy candidate for playing decisive roles in protection against autoimmunity (Chervonsky 2013). For example, Coxsackie B3 viruses can induce type 1 diabetes mellitus in the murine model (Drescher et al. 2004). Demyelinating diseases can be of autoimmune etiology as well and may also have a possible microbial trigger. In the following section, we will try to deliberate more into its details, with specific emphasis on demyelinating diseases, namely acute disseminated encephalomyelitis (ADEM), and also multiple sclerosis (MS).

11.2 Mechanisms of Microorganism-Induced Autoimmunity

Microbes can initiate or precipitate autoimmune disorders in one or many mechanisms. First, a mechanism known as molecular mimicry can be at the very core or heart of autoimmunity. The best example of this and a good example of Group I autoimmunity is acute rheumatic fever. It is a disease caused by the destruction of the myocardium due to the cross-reactivity or molecular mimicry with Group A Streptococcal antigens (Malkiel et al. 2000). *Klebsiella pneumoniae*, for example, is also reported to carry antigens mimicking the MHC class I molecule HLAB27. Hence, it can theoretically induce ankylosing spondylitis (Chervonsky 2013).

Second, it is also possible that the microbe and the host do not have many structurally similar antigens, but there is the induction of co-stimulation and cytokine production by an antigen-presenting cell (APC) which is activated by infection and also presents self-antigens, which may then lead to activation of the autoimmune reaction. This proposed mechanism is also commonly called as "bystander activation" (Esposito et al. 2015).

Third, very relevant to commensal microbiota is the role of specific commensal bacterial lineages in inducing the production of cytokines that can affect the pathogenesis of autoimmunity. The best-known instance is one of the segmented filamentous bacteria (SFB) which stimulate the generation of Th17 and likely also the Th1 types of T-cell responses (Chervonsky 2013). These Th17 cells are critical for defense against certain types of pathogens. They also contribute to the development of autoimmunity. Th17 cells induced by these SFB can affect autoimmune reactions in many remote organs, such as joints (Chervonsky 2013). In this chapter, the authors have tried to present all available information in these aspects in a concise manner.

11.3 Evidence in Illnesses

11.3.1 Demyelinating Disease: Guillain–Barre Syndrome (GBS)

Guillain-Barre syndrome (GBS) or autoimmune demyelinating radiculoneuropathy is an inflammatory disease of the peripheral nervous system which can follow infection with certain microbes like *Campylobacter jejuni*, Epstein–Barr virus (EBV), Cytomegalovirus (CMV), and *Mycoplasma pneumoniae*. Among them, the major infectious agent responsible for the development of GBS is *C. jejuni*. *Campylobacter*, which is the most common cause of bacterial diarrhea in the USA, is a Gram-negative bacillus having a propensity to invade the intestinal mucosal lining (Wucherpfennig 2001). GBS can also occur after CMV infection. CMV-related GBS patients may have a severe course of infection, characterized by a high frequency of respiratory insufficiency, frequent instances of cranial nerve involvement, and severe sensory impairment also. This is in stark contrast to *C. jejuni* infection, which is usually associated with motor GBS (Visser et al. 1996). Studies have found the

presence of high amount of IgM anti-GM2 antibodies in GBS patients following CMV infection (Lunn and Hughes 2011).

11.3.2 Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis is a rare inflammatory disease that affects the brain and spinal cord. It is usually seen in children. It is a transient autoimmune disorder that damages the protective coating of nerve fibers, also called myelin (Melinosky 2020, ADEM). Many names have been used synonymously with ADEM in the scientific literature, like disseminated vasculomyelinopathy, microglial encephalitis, peri-venous encephalitis, peri-venous allergic encephalopathy, allergic neuroencephalopathy, para and post-infectious encephalomyelitis, acute encephalomyeloradiculitis, post-vaccinial encephalomyelitis, as well as acute MS.

ADEM is one of the many categories of primary inflammatory demyelinating disorders of the central nervous system (CNS). Other such diseases are MS, acute transverse myelitis, and Devic's disease. Symptoms of ADEM may be severe but are treatable. Still, scientists are not able to elucidate exactly what triggers ADEM. However, it could be a reaction to an infection. Most of the time, the attack is seen when a child is getting over a common illness, like common cold or gastrointestinal infection. In 50–75% of cases, the beginning of the disease is preceded by a viral or bacterial infection, like usually a sore throat or cough (upper respiratory tract infection). Many different bacteria, viruses, and other sorts of infectious agents have been related to ADEM. However, the disease does not appear to be causally related to any one particular infectious agent or pathogen. Most episodes of ADEM tend to ensue about 7–14 days after the infection.

An ADEM-like disorder was first reported in literature in the eighteenth century, when Lucas J recognized a temporal relationship between neurological problems and smallpox and measles infections (Lucas 1790). Later on, these disorders were recognized to be actually ADEM. At the same time, its association with vaccines, especially, the measles and rabies vaccine, was strongly established (McAlpine 1931). Earlier studies also show a high incidence of neurologic sequelae as well as high mortality rates due to ADEM. For example, there occurs 30% mortality following measles infection (Gibbons et al. 1956). Nowadays the occurrence of ADEM following these events have decreased significantly after successful measles, mumps, and rubella immunization programs and the administration of vaccines free from neural elements. Still, ADEM remains one of the common pediatric demyelinating disorders.

ADEM is the aftermath of an immune reaction following an infection or vaccination in which the immune system, instead of fighting off the infection, leads to inflammation in the CNS (Cleveland Clinic n.d., ADEM). Its clinical course is mostly monophasic. However, relapsing ADEM cases also occur occasionally and may even clinically mimic MS (Javed and Khan 2014). Several viral and bacterial pathogens and various vaccinations were found to be associated with ADEM. Experimental studies indicate that both primary and secondary autoimmune

responses contribute to CNS inflammation and subsequent demyelination. The clinical diagnosis of ADEM is strongly suggested by a close temporal relationship between an infectious incident or immunization and the onset of leukoencephalopathic neurological illnesses (Anilkumar et al. 2021).

11.3.3 Definitions

Historically, acute noninfectious inflammatory demyelinating diseases, which are seen mostly in children, were classified under the umbrella term "ADEM." There was no standard definition of ADEM until recently, when consensus definitions for acquired childhood CNS demyelinating disorders were proposed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) in the year 2007 (Krupp et al. 2007). These definitions were updated in 2013 (Krupp et al. 2013). Diagnosis of ADEM can be achieved only after excluding other possible differential diagnoses. The following criteria should be fulfilled to make a diagnosis of ADEM tenable (also in Table 11.1):

1. First clinical polyfocal CNS insult presumably occurring due to the underlying inflammatory demyelinating disorder.
2. Encephalopathy as suggested by altered sensorium or abnormal behavior which could not be explained by post-ictal events, fever, or any other systemic illness.
3. Abnormalities in brain MRI suggestive of demyelination within 3 months of the onset of disease.
4. No new clinical or MRI abnormalities for 3 months or more after occurrence of the first event.

Table 11.1 Diagnostic criteria for ADEM and relapsing demyelinating disorders (Pohl et al. 2016)

Diagnosis	Clinical criteria
ADEM, monophasic	Single polyfocal CNS event presenting with encephalopathy and which is associated with MRI abnormalities. After the first episode, no new clinical or MRI activity is seen post 3 months
ADEM, multiphasic	After 3 months of the first episode of ADEM, the occurrence of second episode with no further ADEM or non-ADEM demyelinating disease
ADEM-MS	ADEM which is followed by non-ADEM demyelinating relapse after 3 months, along with new MRI abnormalities
ADEM-NMOSD	ADEM followed by events including ON, area postrema syndrome, or extensive transverse myelitis after 3 months meeting MRI requirements according to the revised NMOSD criteria
ADEM-ON	ADEM, MDEM, or multiple ADEM attacks, followed by ON

Abbreviations: *ADEM* acute disseminated encephalomyelitis, *MDEM* multiphasic disseminated encephalomyelitis, *MS* multiple sclerosis, *NMOSD* neuromyelitis optica spectrum disorder, *ON* optic neuritis

11.3.4 Epidemiology

Even though it is thought to be an uncommon illness, the worldwide prevalence of ADEM is an estimated 1 in 125,000–250,000 individuals per year. This disease has an approximate annual incidence of 0.8 per 100,000 people, with a median age of onset of 6.5 years. Most of the cases are seen in children, mostly younger than age 10 years, and the remaining between the ages 10 and 20 years. However, ADEM has been also found in adults between the ages 18 and 82 years. Many studies have shown that ADEM is quite rare in the elderly population, with 83% of patients being lesser than 50 years of age (Madan et al. 2005; Maramottom and Sarada 2006). In a study by Javed and Khan, the median age of affection in adults was found to be 33–41 years. Most of the cases were seen in children aged 5–8 years and in adults aged 19–61 years (Javed and Khan 2014).

Most commonly, measles virus infection is followed by ADEM, as seen in about 1 in 1000 cases. Incidence of ADEM after varicella zoster virus (VZV) are said to be 1 in 10,000 and rubella infections are said to be 1 in 20,000. This disease occurs more commonly in males than in females. In fact, it shows a male to female ratio of 1.3:1. In adults, ADEM is found more commonly in males as compared to females, although this gender difference is not so marked in cases of children. It is reported more often seasonally, in winter and spring. The true incidence of this disease in India is basically undetermined. It is possibly more frequent than has been reported. This is because the common antecedent events like exanthematous fever and Semple anti-rabies vaccination, all of which can predispose to ADEM, are still quite commonly found in our country (India). Generally, vaccine-induced ADEM is thought to be rarer as compared to postinfectious ADEM. Over and above, 95% of cases of ADEM take place after infections, and only about 5% can be attributed to postvaccination.

11.4 ADEM and Microbial Link

ADEM can occur after infection by a variety of microorganisms like viruses, bacteria, and parasites. The infectious etiology of ADEM is also supported by the seasonal variation seen in the occurrence of ADEM cases. This is because peak incidence of ADEM is seen during winter and spring months. The most common microorganisms associated with ADEM include CMV, Epstein–Barr virus (EBV), herpes simplex virus (HSV), human herpes virus-6 (HHV-6), influenza virus, hepatitis A, human immunodeficiency virus (HIV), and *Mycoplasma pneumoniae*. A detailed description of each of these is given below.

11.4.1 Viral Causes

The earliest association of ADEM was demonstrated with virus infections like measles and smallpox. Various other viruses like coronaviruses, dengue virus, and

coxsackievirus can also be responsible for it. However, ADEM is causally linked with viral infections of the gastrointestinal or respiratory tracts (Anilkumar et al. 2021). The viral agents as potential winter and spring respiratory pathogens includes the influenza virus, respiratory syncytial virus (RSV), and coronavirus, but only the H1N1 influenza virus is associated with the winter/spring respiratory illness pattern seen in ADEM. Viral infections associated with ADEM include measles, mumps, rubella, VZV, EBV, CMV, HSV, hepatitis A, and coxsackievirus. There has been an increased incidence in association with rubeola, rubella, mumps, varicella, and smallpox also. Before the development of immunization programs, ADEM was most commonly associated with measles with an incidence of 1–2 per 1000 episodes of measles infections (Gibbons et al. 1956). Among the category of postmeasles neurologic complications, ADEM stands first, comprising about 95% of the total complications. The remaining 5% consists of effects like myelitis, polyneuritis, and toxic encephalopathy.

As compared to measles, neurologic complications associated with VZV infection are less commonly seen (1:10,000 infections). The two major neurologic complications linked with VZV infection are acute cerebellar ataxia and acute toxic encephalopathy (also called Reye's syndrome). The former has a very good prognosis, whereas the latter one can have fatal outcome. Kobayashi et al. have described the role of rotavirus in ADEM in two children who had rotavirus diarrhea (Kobayashi et al. 2010). In HIV-infected patients, ADEM develops generally as a multifocal disorder affecting the CNS. It becomes monophasic during seroconversion. This occurs even when the immune system remains competent. A case series of seven HIV-infected patients with mild to moderate immunosuppression was published by Naidoo et al. (2017). The authors supposed that marked immunosuppression (CD4 $<$ 200 cells/μL) and normal CD4 counts (CD4 $>$ 500 cells/μL) might be responsible for causing these atypical presentations. Acute hemorrhagic leukoencephalomyelitis (AHLE) typically follows an attack of influenza or upper respiratory infection.

11.4.2 SARS-CoV-2 and Other Coronaviruses

ADEM can exist at the severe extreme end of the spectrum of neurological manifestations in SARS-CoV-2 infection as well. Clinically, it presents as a nonspecific acute-onset encephalopathy that can manifest as behavioral change or alteration in the consciousness, with or without fever. ADEM has been described in association with Middle-East Respiratory Syndrome coronavirus and Coronavirus type OC43 also. Langley et al. (2020) reported a case of ADEM which occurred along with COVID-19 pneumonia in a 53-year-old man presenting with complaints of cough, dyspnea, fever, myalgia, and malaise. The SARS-CoV-2 receptors are expressed in CNS tissue. SARS-CoV-2 infection may result in a wide range of neurological diseases. These may occur through direct infection, para-infectious complications, or even due to the associated critical illness itself (Paterson et al. 2020).

A recent systematic review, which included 409 patients from the seven relevant studies, has shown that the neurological manifestations were found in 17.3–36.4% of cases after SARS-CoV-2 infection; in children, encephalitis was also quite commonly seen as a respiratory disorder (Correia et al. 2020). In their review, common probable diagnoses were acute viral meningitis/encephalitis (6.1%), hypoxic encephalopathy (5.6%), acute cerebrovascular diseases (1.4%), GBS (1.4%), and ADEM and acute necrotizing hemorrhagic encephalopathy in one (0.2%) patient (Correia et al. 2020). Montalvan et al. also showed that the SARS-CoV-2 infection can present as encephalitis, demyelination, neuropathy, and stroke. Some of the proposed mechanisms responsible for the neurological manifestations of COVID-19 include trans-synaptic transfer and invasion through the cribriform plate and olfactory bulb (Montalvan et al. 2020).

Another recent systematic review presented epidemiological and clinical evidence of 30 cases (9 pediatric and 21 adult cases) of ADEM associated with COVID-19 reported globally. The authors showed that moderate and severe ADEM was associated with poorer outcomes; however, no association had been found between COVID-19 severity and ADEM severity (Fisher's exact $p = 0.99$), or treatment type and clinical outcome at discharge ($p = 0.99$). They concluded that in patients recovering from COVID-19, ADEM should be suspected in the presence of multifocal neurological features with or without encephalopathy (Zelada-Ríos et al. 2021).

11.4.3 Bacterial Causes

Bacteria like *Borrelia*, *Legionella*, *Chlamydia* spp., and *Leptospira* are also responsible and can be implicated in the occurrence of ADEM (Menge et al. 2005). The main bacterial trigger for ADEM seems to be *Mycoplasma pneumoniae*. Other bacterial infections like *Borrelia burgdorferi*, *Leptospira*, and Group A β-hemolytic *Streptococci* have also been implicated. *Rickettsia* spp. can also cause ADEM; also, there are reports of ADEM occurring after scrub typhus. ADEM cases have also occurred after gastroenteritis by *Campylobacter* spp. *Legionella cincinnatiensis* can cause Pontiac fever which can also lead to ADEM. Rarely, ADEM can even be the presenting feature of CNS tuberculosis. Mediastinal tuberculosis has also been reported to cause ADEM in infants. Yang et al. recently reported a case of a 7-month-old female infant who presented with acute onset encephalopathy and left focal weakness in the setting of 3 months of nonproductive cough (Yang et al. 2021). TB infection with associated encephalitis and myelitis was seen, and the neuroimaging was consistent with an acute demyelinating process. The authors concluded that diagnosis of ADEM should be considered in a child having multifocal neurological symptoms, pulmonary TB, and associated evidence of demyelination on MRI. Hence, *Mycobacterium tuberculosis* should also be considered an important bacterium here. ADEM can take place after pulmonary tuberculosis also.

11.4.4 Parasitic Causes

Parasitic infection can also rarely lead to complications like ADEM. *Plasmodium falciparum* infection can be associated with ADEM, generally about 43–45 days following parasitic cure (Agrawal and Goyal 2012). Very rarely, *Plasmodium vivax* can also lead to ADEM in children. In the pediatric literature, the only single case of ADEM following treatment of *Plasmodium vivax* malaria has been reported by Sidhu et al. (2015) in an 8-year-old female child having abnormal choreoathetoid movements and ataxia after recovery from *P. vivax* infection. The diagnosis was made on the basis of MRI, and the treatment was started with corticosteroids. It has also been noted after CNS toxoplasmosis, particularly in children.

11.4.5 Vaccination-Induced ADEM

Most of the cases of ADEM occur following infection. However, about 5% of the cases can occur after vaccination. Postvaccine ADEM can be found approximately 1–3 weeks after immunization in children as well as in adults. Rabies (Semple) vaccine was the earliest reported vaccine to be associated with ADEM. It was reported more due to the nerve tissue present in the vaccine. In patients receiving Pasteur's rabies vaccine, introduced in 1885, ADEM-like cases were observed in approximately 1 in 1000 recipients. In countries where neural tissue-based vaccines are still in vogue, anti-rabies immunization consisting of either BPL (-β-propiolactone inactivated) or Semple (phenol inactivated) vaccines are also important causes for ADEM. Neuroparalytic accidents in patients receiving Edward Jenner's smallpox (actually cowpox) vaccine have also been reported after its widespread introduction in 1853. When smallpox vaccination was a part of the universal immunization program, encephalomyelitis cases occurred in one out of 4000 vaccinations. Other less common vaccines associated with ADEM are those for measles, pertussis, tetanus, influenza, hepatitis B, rubella, diphtheria, *Streptococcus pneumoniae*, varicella, smallpox, human papillomavirus (HPV), and polio vaccine (Pellegrino et al. 2013).

Vaccine-induced ADEM events occur generally within weeks of vaccination, but can take even up to 3 months to occur. The Collaborating Center for Reference and Research on Viral Hepatitis of the World Health Organization (based in Geneva, Switzerland) has deemed a maximum period of 3 months to diagnose and define a vaccine-associated ADEM (Menge et al. 2005). ADEM has also developed following TdaP vaccination in adults, and many such cases are reported in the literature. Aggressive ADEM cases may follow after HPV vaccination. Data from the US-based Vaccine Adverse Event Reporting System and European Union-based EudraVigilance safety databases show that along with the HPV, the vaccines against seasonal influenza and H1N1 are most commonly reported to be associated with the onset of acute disseminated encephalomyelitis.

Rarely, yellow fever vaccination can also lead to the destruction of myelin and ADEM. Very few case reports were published in the literature related to ADEM after

vaccination. Soares et al. (2018) reported the case of ADEM after yellow fever vaccination in a 17-year-old female who presented to the emergency department with complaints of fever, paraparesis, and urinary retention after 31 days of yellow fever immunization. The MMR vaccine can also very rarely trigger the condition. ADEM has also been reported after SARS-CoV-2 vaccination in adults. The first dose of vaccination is usually associated more commonly with ADEM than re-vaccination or booster doses.

Some of the vaccine-associated ADEM cases can be directly linked to the contamination of the specific vaccine with CNS tissue. This contamination can explain the huge 0.15% incidence of ADEM after immunization with a live attenuated rabies virus vaccine (Semple vaccine) in developing countries, which is propagated in cultures of rabbit or goat CNS tissue. In this regard, it is important to mention that antibodies against myelin antigens are detectable in patients with Semple vaccine-associated ADEM (Menge et al. 2005). Newer rabies vaccines are propagated in human diploid cells (HDCC) and hence do not cause this particular adverse effect. A similar mechanism may account for ADEM observed after vaccination against Japanese B encephalitis, where certain vaccine strains are propagated in mouse brains. ADEM after malaria is due to a lag in immune response occurring after malaria. This leads to secondary infection by many microorganisms that can lead to ADEM.

11.4.6 Other Causes of ADEM

Reports of ADEM following solid organ transplantation are there but quite rare. These include a case report published by Caucheteux et al. (2013) among two renal transplant patients in which EBV was identified as the main culprit responsible for ADEM. Aboagye-Kumi et al. (2008) reported an unusual case of a 34-year-old white female with ADEM developing 5 years after a living-related renal transplant. Also, microbes or vaccines are not the only causes of ADEM. There are also cases describe in the literature of ADEM following repeated injection of herbal extracts.

11.5 Pathogenesis of ADEM

The exact mechanism of ADEM is incompletely understood till now. However, it is said to result from inflammation which is triggered by environmental stimuli like vaccination or infectious diseases in genetically susceptible persons. ADEM has been characterized as an autoimmune disorder which causes demyelination in the CNS. Although there is a temporal relationship between fever due to infections and the beginning of neurologic symptoms, the neurologic illness is possibly not caused due to direct invasion by the infectious agent of the CNS. This is because: (a) no infectious agent has been consistently found in the CNS in the affected individuals by cerebrospinal fluid (CSF) analysis, brain biopsy, or postmortem analyses, (b) the lesions of acute viral encephalitis are different from ADEM, and (c) similar clinical

illness with ADEM can be encountered after vaccination with non-viable viruses. Hence, it is likely that the microorganisms which are implicated, trigger an autoimmune response against the CNS antigens, which in turn leads to the CNS pathology and disease (Javed and Khan 2014).

It has been suggested that either a cell-mediated response or antibodies produced in response to an environmental stimulus can cross-react with the host's myelin autoantigens present in the CNS to produce ADEM. These myelin autoantigens like the myelin basic protein (MBP), proteolipid protein, and myelin oligodendrocyte glycoprotein (MOG) can possess many antigenic determinants resembling those of the infecting pathogen. This leads to the demyelination which is characteristically found in ADEM. These cross-reactive T cells can multiply in response to self-antigenic stimulation and produce various chemokines. These chemokines can further recruit more lymphocytes and macrophages at the site of immune activation. This then further enhances demyelination and neuronal and axonal injuries. Autoantibodies directed against MOG are found in about 36–64% of children who have ADEM. These antibodies against MOG have been found to induce complement-mediated cytotoxicity. Their titers do correlate well with the extent of antibody-dependent cell-mediated cytotoxicity and an increased level of complements. The most common isotype of MOG antibody seen in ADEM is IgG1, which can fix complement and also bind to Fc receptors.

Another proposed mechanism is that ADEM can occur as a consequence of increased vascular permeability and congestion in the CNS, due to the inflammation and circulating immune complexes seen after vaccination or infection. Mononuclear infiltration in the vasculature of the CNS is believed to result in edema around blood vessels and occasionally hemorrhage causing damage to surrounding nerve cells (in the form of demyelination, necrosis, or gliosis). This ultimately leads to the variety of possible clinical presentations and prognoses which are seen in persons with ADEM (Javed and Khan 2014).

A third proposed mechanism is the generation of myelin-reactive T cells via nonspecific activation of naturally occurring autoreactive T cells by viral or bacterial "superantigens." Such foreign antigens are able to activate a wide variety of $CD4^+$ T cells. Some of these may have some reactivity against nerve myelin epitopes. Upon activation, these T cells can multiply and help generate a brisk inflammatory response to self-antigens. For example, in post-*Streptococcus*-related ADEM cases, superantigens seen in *Streptococcus pyogenes* cell walls may nonselectively activate T cells.

ADEM may also happen from the activation of previously primed immune reactive cells after reinfection by the same microorganism. Both $CD4^+$ and $CD8^+$ T cells have been implicated in this type of secondary autoimmune response; astrocytes and microglia in the CNS can act as antigen-presenting cells (APCs). Direct infection of these cells by some viruses can lead to activation of a proportion of T cells that were primed in the initial infectious event with the same microorganism. These previously primed T cells can subsequently mount a robust inflammatory response against the CNS epitopes like myelin.

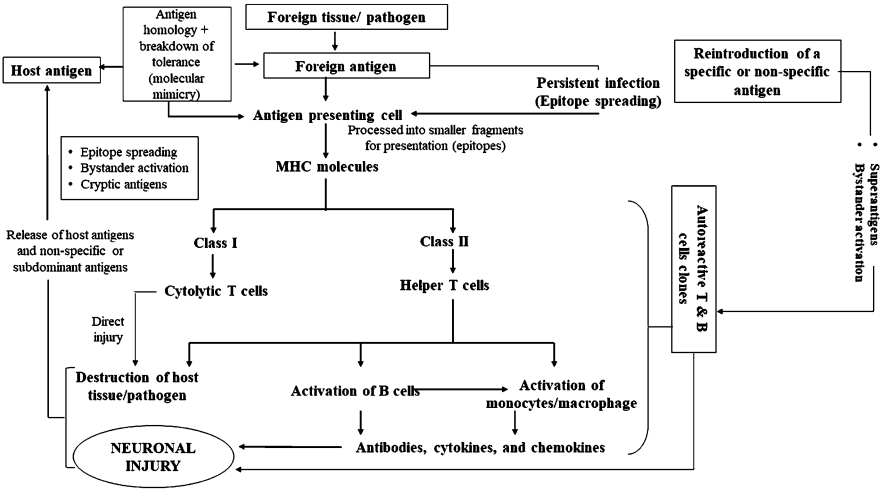

Fig. 11.1 Mechanism of immune-mediated injury in ADEM (Garg et al. 2016)

Lastly, the host genotype is also no less important for predisposition to ADEM. The host haplotype DRB1 is associated with more number of cases of ADEM as compared to other haplotypes. Mutations of the *SCN1A* gene have also been significantly associated with postvaccine encephalopathy and ADEM. The proposed mechanisms of immune-mediated injury in ADEM is shown in Fig. 11.1.

11.6 ADEM and Gut Microbiota

The human gastrointestinal (GI) tract shelters a wide variety of microorganisms, known as the gut microbiota. This exerts a marked influence on the host during homeostasis and disease. The gut microbiota is characterized by a large number as well as a wide variety of the microorganisms, and their interdependence with each other and also with the host. The gut ecosystem is colonized by about 10^{14} microbes, which is ten times more than the human cells. The human body harbors 500–1000 bacterial species at any given point of time. Out of them, 100–200 species reside in the gut alone (Turnbaugh et al. 2007). In the Human Microbiome Project, researchers had isolated the microbiome from 15 to 18 anatomic sites in a total of 250 healthy American adults. They found the presence of different microbiota in different body sites apart from a wide interindividual variation (Human Microbiome Project Consortium 2012).

Apart from being critical for many elements of human physiology, the gut microbiota has also been shown to play an important role in the pathogenic mechanism of many diseases. There is well-recognized bidirectional system of communication between the gut and brain, which is known as the gut–brain axis. The gut microbiota not only regulates the GI tract, but also plays a crucial role in brain

development and function. Recently, the concept of the microbiome–gut–brain axis has reemerged, because studies have demonstrated a specific role of the gut microbiota in the gut–brain axis in affecting functions of CNS through multiple neurocrine and endocrine signaling pathways. Many physical and psychological factors can also influence the composition and metabolic activities of the gut microbiota, while changes in gut microbiota have also shown to shape various brain activities. The microbiome can thus influence the CNS functions in both normal and disease states (Sharon et al. 2016; Wang and Kasper 2014).

The gut microbiota may influence brain health in the following means: (1) Stimulation of the innate immune system by the bacterial components such as lipopolysaccharides. It is a normal phenomenon. However, any dysbiosis can lead to excessive stimulation and may culminate in systemic and/or CNS inflammation. (2) Cross-reactivity of the bacterial proteins with human antigens may lead to an abnormal response of the adaptive immune system. (3) Neurotoxicity caused by the metabolites such as ammonia and D-lactic acid produced by the bacterial enzymes or even by beneficial metabolites such as short-chain fatty acids. (4) Production of hormones and neurotransmitters by the gut microbes identical to those produced by humans, which may influence the microbial growth and virulence. (5) Direct stimulation of the enteric nervous system by the gut microbiota may be able to send signals to the brain by stimulating the vagus nerve (Wang and Kasper 2014; Sharon et al. 2016).

Previous studies have firmly established the vital role of the gut microbiome in many basic neurogenerative processes such as neurogenesis, myelination, formation of the blood–brain barrier, and microglial maturation, as well as in modulating behavior. They also affect the activity of the hypothalamic-pituitary-adrenal axis and influencing memory, mood, and cognition. A complex interaction between many factors like genetic, epigenetic, and environmental factors influences these effects on human neurodevelopment and behavior. Dysbiosis, any changes in the normal microbiota, is the first step to disinhibit the growth of pathogenic organisms and the development of a disease. Dysbiosis has been shown to be associated with many inflammatory disorders, such as arthritides, inflammatory bowel disease, cancers, and a few neurological disorders.

Although epidemiological studies demonstrating the role of the microbiome with CNS pathologies are somewhat lacking, many experimental studies have stressed upon the importance of the microbiome in many CNS disorders (Glenn and Mowry 2016). These disorders can be classified as immune-mediated (like multiple sclerosis) and non-immune-mediated (like neuropsychiatric disorders such as autism, depression, anxiety, and stress). Studies using the experimental autoimmune encephalomyelitis (EAE), a T-cell-mediated experimental model for MS, have for the first time described the role of the gut microbiota in the pathogenesis of autoimmune CNS diseases (Ochoa-Reparaz et al. 2009). Although no such study is available directly which shows a relation of the gut microbiota with ADEM, the same has been demonstrated for MS, in a few case–control studies. MS is a relapsing demyelinating disease.

Cantarel et al. (2015) showed a decrease in the levels of Bacteroidaceae, Faecalibacterium, and *Ruminococcus* in persons with MS. Another study has demonstrated higher levels of the colonic anaerobes Archaea; especially, *Methanobrevibacter smithii* in patients with MS than in controls (Jhangi et al. 2014). Miyake et al. (2015) did a similar study on Japanese MS patients and found an increase in Actinobacteria, *Bifidobacterium*, and *Streptococcus* species and a decrease in Bacteroidetes, Firmicutes, Faecalibacterium, *Prevotella*, and *Anaerostipes* species in MS patients compared to controls. However, these studies were small, and thus, it is not possible to generalize these results across various populations.

The Gram-negative bacterium, *C. Jejuni* which is considered as one of the most common causes of gastroenteritis, has also been causally linked to ADEM. Marziali et al. (2017) have reported a case of a 25-year-old male with a diagnosis of ADEM following gut infection with *C. jejuni.* This patient presented with gastroenteritis, urinary retention, and various neurological symptoms such ataxic gait, paresthesia, hypoesthesia, and VIIth cranial nerve palsy (Marziali et al. 2017). Gastrointestinal infection occurring due to adenovirus has also been shown to present as ADEM, apart from other neurological complications like encephalitis, febrile seizures, and aseptic meningitis (Schwartz et al. 2019). Though animal studies have shown strong evidence of the role of the gut microbiota in CNS homeostasis, studies in humans, for evaluating their interactions with CNS, are still in a nascent stage.

11.7 Pathological Findings of ADEM

The pathognomonic lesion seen in ADEM is multifocal perivascular inflammation, with infiltration of lymphocytes and macrophages seen in the CNS parenchyma (Javed and Khan 2014). This perivenous demyelination is not found in other demyelinating disorders like MS. In fact, MS shows more confluent demyelination. ADEM is characterized by inflammation occurring mainly in the Virchow-Robin spaces. There can be diffuse and often symmetric perivenular demyelination. These lesions are of similar histological age. They are more commonly found in the white matter but can also involve the deeper cortical laminae, thalamus, hypothalamus, and other parts of the gray matter. In the brain and neural tissues, edema is the hallmark feature of ADEM. This is understandable, given the plausible etiopathogenesis. Viral inclusion bodies are not observable on hematoxylin and eosin-stained sections. Histologic findings reveal inflammatory demyelinating lesions, which typically occur in the spinal cord and also in the brain in some animals.

Taking into account the extent of perivascular inflammation in ADEM, some scientists suggest that ADEM is possibly a type of vasculopathy with secondary myelin destruction. Adjacent to the areas of inflammation, myelin loss can occur with characteristic relative axonal sparing. Histological staining for myelin basic protein and MOG shows loss of these two myelin proteins. Demyelination also often involves the cortex–subcortical matter junction. Demyelination may not be so evident in hyperacute or acute lesions of ADEM, but can develop later on in the

lesions. Often they evolve in a pathognomonic "sleeve-like" manner, confined to the hypercellular areas.

The characteristic findings of AHLE are multifocal petechial hemorrhages distributed diffusely all throughout the brain. The pathological findings found in ADEM are somewhat identical to experimental allergic encephalomyelitis (EAE). EAE is an autoimmune encephalomyelitis that can be induced experimentally in susceptible animals by exposure to several myelin antigens like MBP, proteolipid protein, and MOG.

11.8 Clinical Features of ADEM

The ADEM syndrome develops commonly within 6 days to 6 weeks following any infectious episode. The common systemic symptoms of ADEM are fever, lassitude, mental confusion, dysphagia, nausea, and vomiting. Among neurological signs, encephalopathy (or altered consciousness) is the hallmark feature of ADEM. However, its absence does not in any way preclude the diagnosis of ADEM. Approximately 20–52% of adult ADEM patients present clinically with encephalopathy. On the contrary, in childhood cases, fever (15%), meningism (15%), loss of consciousness (19%), and seizures (4%) are uncommon (Javed and Khan 2014). Along with motor and sensory deficits like paraparesis and tetraparesis, patients may also present with brainstem anomalies like dysarthria or oculomotor dysfunction. There may be other neurologic abnormalities too, in the form of seizures, ataxia, aphasia, nystagmus, optic neuritis, urinary retention, increased intracranial pressure, or extrapyramidal signs. Some reports have also shown multiple cranial nerve involvement, especially optic nerve involvement along with optic disk edema.

Similar clinical features such as neck pain, neck rigidity, or neck stiffness can lead to confusion in distinguishing ADEM from meningoencephalitis. Most frequently, ADEM is mistaken as meningoencephalitis in children (National Organization for Rare Disorders n.d., ADEM). Myelitis with urinary dysfunction is notable in about 25% cases of ADEM. Signs and symptoms of peripheral nervous system involvement include paresthesia or anesthesia of the limbs or muscular atrophy. These patients generally have a worse prognosis and also increased risk of relapse as compared to those with only CNS involvement (Anilkumar et al. 2021). ADEM is usually monophasic, but recurrent forms of demyelination like multiphasic ADEM (MDEM) and ADEM followed by recurrent Optic neuritis (ADEM-ON) are also commonly reported in the scientific literature. In Eastern India, ADEM is now considered an important etiology behind acute encephalitis syndrome (AES).

Weston–Hurst disease or AHLE is considered to be a more fulminant form of ADEM. AHLE is common in all age groups; it manifests by abrupt onset of symptoms and signs. AHLE is often associated with rapid deterioration and life-threatening complications such as cerebral edema as soon as 1 week after onset. Despite this severe and rapid course, there have been reports of favorable neurological outcomes of AHLE in individuals who are treated early and effectively (NORD, ADEM). Its clinical course is monophasic. Also, it is rarer than ADEM, found in

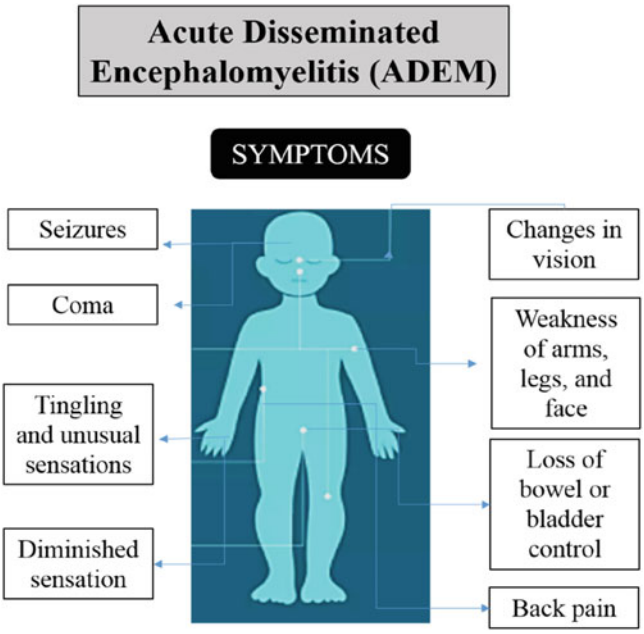

Fig. 11.2 Clinical features of ADEM (Moawad 2019)

about 2% of children with ADEM (Krupp et al. 2013). The clinical features of ADEM are shown in Fig. 11.2.

11.9 Diagnosis of ADEM

ADEM is actually a clinical diagnosis. It is, in fact, often a diagnosis of exclusion. There is no clear-cut biological marker for the disease; diagnosis is hence based mainly on clinical findings and is often carried out with the aid of neuroimaging.

11.9.1 Neuroimaging

A temporal relationship like occurrence after infection or vaccination strongly suggests the possibility of ADEM. It is usually also confirmed by neuroimaging. Particularly, magnetic resonance imaging (MRI) scan is very helpful in this aspect (Krupp et al. 2013). Also, the brain and spinal cord MRI scans are of immense use for differentiating ADEM from other demyelinating diseases like MS. MRI shows mostly asymmetric hyperintense lesions upon T2-weighted, fluid-attenuated inversion recovery (FLAIR), proton density, and echo-planar trace diffusion sequence imaging (Figs. 11.3 and 11.4). The spinal cord may reveal confluent lesions on MRI.

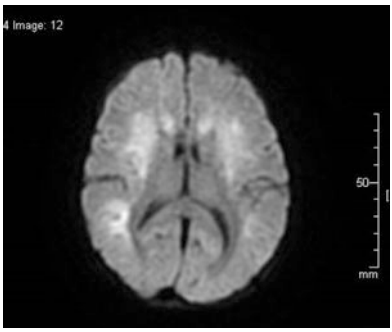

Fig. 11.3 MRI brain: Diffusion-weighted images, showing asymmetrical hyperintense signals involving bilateral periventricular white matter, centrum semiovale, and genu of the corpus callosum

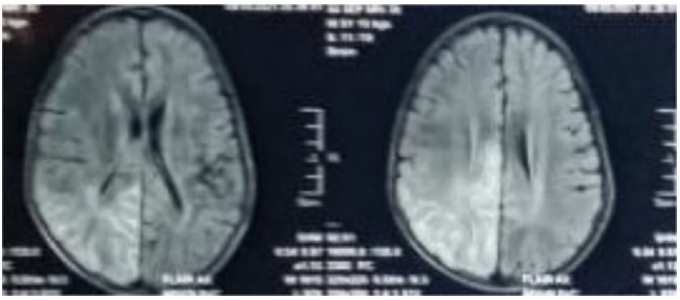

Fig. 11.4 MRI brain: T2WI sequence axial image showing multiple patchy hyperintensities in bilateral parieto-temporal-occipital lobes involving cortical and subcortical white matter and bilateral globus pallidus

Diffusion-weighted image (DWI) with restricted diffusion and a parietal ring-enhancing lesion following IVG gadolinium administration can also be found in ADEM, especially, after HIV infection.

Involvement of the cerebellum and brainstem is more commonly seen in children, which can also be evident in MRI. This is because often the lesions in ADEM can evolve over few weeks. Specific viruses can show different MRI patterns. In the post-varicella zoster ADEM with cerebellitis, the MRI findings are generally normal. In some cases, typical MRI findings may also appear weeks after the onset of symptoms (Anilkumar et al. 2021). CT or MRI scan of a patient with AHEM or AHLE can reveal focal hemorrhagic lesions, together with edema, petechial and perivascular hemorrhages, blood vessel destruction, fibrin deposition, and neutrophilic infiltration. MRI scans can show small areas of reduced T2 signaling due to hemorrhages. Diffusion restriction can also be found in the acute stages of AHLE. However, DWI is not reliable in the presence of hemorrhage.

11.9.2 CSF Analysis

CSF findings can also help in clinching the diagnosis of this disease. CSF findings in ADEM patients can be nonspecific, but are abnormal in about 67–70% of the cases. These abnormal findings include lymphocytic pleocytosis along with raised protein levels and sterile cultures. CSF protein level is mildly elevated, up to the tune of <70 mg/dl. CSF examination can even be normal in 19–33% of the adults having ADEM. Also, in cases of ADEM occurring after pulmonary TB, the CSF findings are usually normal. Oligoclonal bands (OCBs) are usually not present in CSF in cases of ADEM and their presence is mostly associated with relapsing disease. Their presence, however, is reported in about 90% of MS patients but they are rarely detected in other forms of CNS demyelination like ADEM and neuromyelitis optica (NMO) (Sonneville et al. 2009). Patients with ADEM are often found to have elevated MBP on CSF analysis as well. This is indeed an indication of demyelination occurring in the CNS. Brainstem lesions are more commonly found in children. AHLE also has almost the same CSF findings as ADEM; here a large number of RBCs can be found in the CSF, as a reflection of the microhemorrhagic process.

11.9.3 CNS Angiography

Angiography is characteristically normal in ADEM patients, but can show some abnormalities in patients with moderate-vessel to large-vessel vasculitis. In all the cases of unexplained encephalopathy with multifocal areas of increased signals of the CNS, white matter, brain biopsy should hence be carried out.

11.9.4 EEG

Generalized slowing is the most commonly observed finding seen in electroencephalography (EEG) in ADEM; it is usually nonspecific. This slowing is an indication of the underlying inflammatory process. EEG carried out on a patient with ADEM can also yield results like a disturbed sleep pattern, and either focal or generalized slowing of electrical activity. At times, specific EEG pictures like spindle coma patterns and alternating patterns have also been noted. However, due to low sensitivity and specificity, EEG is not generally used for diagnosis of ADEM. However, it can be of help during seizures, because it helps in assessing the prognosis.

11.9.5 Serological Tests

Serology has also been tried for diagnosis of ADEM in the form of IgM antibody detection against ganglioside antigens by ELISA. The rise or fall of titers has a diagnostic value. Scientists have also reported consistent anti-Aquaporin 4 antibody positivity in ADEM, particularly in children and young adults. In case of ADEM

following *Legionella* infection, diagnosis can be achieved by PCR from CSF. In cases of ADEM after infection taking place due to this bacterium, urinary antigen tests for *Legionella* can also be positive (Krupp et al. 2013).

11.9.6 Multiphasic Disseminated Encephalomyelitis (MDEM)

Recurrent episodes of ADEM in which the episodes differ clinically are termed MDEM. In some cases of ADEM, the premature stoppage or tapering of therapy can lead to recurrence of symptoms. The following criteria are very important when differentiating MS and MDEM (Krupp et al. 2013):

(a) Altered mental state, relapses more than 3 months apart, rapidly evolving neurological deficits, and fast, complete recovery favor a diagnosis of MDEM. Diplopia and asymmetrical deficits usually indicate MS.
(b) The number, morphology, and distribution of lesions on MRI, with lesions >1 cm or involving the cortical ribbon or thalamus, or located infratentorially, and the later disappearance of T2 abnormalities, are quite distinctive of ADEM and MDEM. The subsequent development of new lesions on MRI is, on the other hand, quite pathognomonic of MS.
(c) Marked CSF pleocytosis and a normal IgG index are found more often in ADEM and are very rare in MS.
(d) Bilateral prolonged visual evoked potentials (VEPs) with no history of optic neuritis occur usually in MS, but are not generally seen in ADEM.

Clinicians are also advised to avoid immunization for at least 6 months after the diagnosis of ADEM because relapse into MDEM can occur following resumption of routine vaccination. HHV-6 is now considered to be a very important cause behind MDEM cases (Novoa et al. 1997).

11.9.7 Differential Diagnosis

Other forms of encephalitis that can also cause demyelination but are clinically and pathologically different from ADEM are (a) subacute sclerosing panencephalitis (SSPE), a chronic progressive infection of the brain by the measles virus, (b) rubella panencephalitis, (c) VZV encephalitis, and (d) HHV-6 infection of the CNS (Javed and Khan 2014). No specific criteria are present for diagnosing ADEM, but the antecedent history of infection and fever, temporal course of illness, typical neuroimaging findings, CSF analysis, and repeat imaging during remission are indeed the most important tools for clinching the diagnosis and to help exclude the other causes of encephalopathy (Javed and Khan 2014). Most commonly, physicians confuse ADEM with MS and NMO.

The initial presentation of ADEM is really very similar to that of MS. Features that indicate MS are: a relatively benign clinical presentation, MRI lesions

concentrated more or less around the periventricular and pericallosal areas, MRI findings showing chronic lesions (T1 lesions), absence of gray matter lesions, and profuse and persistent oligoclonal bands (OCB) in CSF. The transient appearance of oligoclonal bands is not very rare in ADEM, but exceedingly rare in MS. ADEM lesions typically show indistinct margins on MRI imaging. This may help in differentiating ADEM lesions from the clear-cut margins of the lesions typically seen in MS. The MS is commoner in females while ADEM is seen more often in males as per scientific data. Also, children are more susceptible than adults to develop ADEM, but MS is a rare diagnosis in children (Krupp et al. 2013).

Optic neuritis (ON) can occur both in ADEM and MS. ON is frequently bilateral in ADEM, but typically unilateral in MS. Bilateral optic neuritis and transverse myelitis are usually suggestive of demyelinating diseases like ADEM. The corpus callosum of the brain is affected commonly in MS, but very rarely in ADEM (Garg 2003). Symptoms of ADEM like fever, headache, confusion, vomiting, and seizures are not usually encountered in persons with MS, but they can be noted rarely in pediatric MS cases, especially in patients younger than 11 years of age. The presence of older brain lesions on MRI suggests that the condition may be more likely to be MS rather than ADEM, because MS can cause brain lesions before symptoms become evident. Bilateral optic neuritis is to be seen more frequently in ADEM than in MS.

Gadolinium-enhanced MRI may also help to distinguish these two demyelinating disorders. A mixture of enhancing and non-enhancing lesions usually indicates temporal dissemination of MS. Lesions in the thalamus of the brain are more often seen in ADEM rather than MS (Murthy 2002). On the other hand, periventricular lesions are commoner in cases of MS. The difference between ADEM and MS is delineated in Table 11.2. The features that favor a diagnosis of NMO or Devic's disease over ADEM include features of concurrent extensive transverse myelitis and severe unilateral or bilateral optic neuritis with no evidence of involvement of any other part of the CNS (Javed and Khan 2014).

Other diseases should also be considered in the differential diagnosis of ADEM, like infectious meningoencephalitis, antiphospholipid antibody syndrome (APS), primary isolated CNS angiitis, vasculitis, CNS metastasis of tumors, and neurosarcoidosis (Ozden and Togan 2016). Sometimes neurocysticercosis and porphyria may also mimic ADEM clinically as well as in MRI. Acute intermittent porphyria can also be a rare cause of ADEM (Sheikh et al. 2018). Toxocariasis, i.e., human infection by *Toxocaracanis* or *Toxocara catis*, particularly in children or adolescents, can be associated with development of encephalopathy. Its imaging pattern has often overlapping features with that of ADEM, with gadolinium enhancement. Children are at risk of accidental ingestion of prescription drugs, illicit substances, alcohol, and many household products that can cause acute encephalopathy associated with other neurological symptoms, that sometimes closely mimic ADEM.

Table 11.2 Differences between ADEM and multiple sclerosis (Javed and Khan 2014; Sheikh et al. 2018)

Parameter	ADEM	Multiple sclerosis
Age	Children	Adults
Gender	Male > female	Female > male
Oligoclonal bands in CSF	Rare and transient	Common and persistent
Lymphocytic pleocytosis in CSF	Common	Rarely seen
Nature of disease	Single or monophasic	Relapsing and recurrent episodes
White matter lesions	Common	Not found
Lesions in thalamus	Commonly seen	Rare
Symptoms like fever, headache, vomiting, and confusion	Frequently present	Not found
Older brain lesions on MRI	Very rare	Frequently found
Periventricular plaques, ovoid lesions, and black holes on T1-weighted MRI	Not found	Commonly found

11.10 Treatment of ADEM

The goal of therapy in ADEM is to check the inflammation quickly and to stop the immune system-mediated attack on nerve myelin. Usually, active infection has to be ruled out before instituting such immunosuppressive form of therapy. Corticosteroids and intravenous immunoglobulin (IVIG) are the mainstays of the treatment; although there is no accepted universal treatment regime. Survival in ADEM cases has increased now, due to the timely use of potent corticosteroids like methylprednisolone. Methylprednisolone is the corticosteroid of choice in ADEM and is used intravenously in a dose of 10–30 mg/kg/day, up to a maximum of 1 g/day for 3–5 days.

The justification for corticosteroid use is its ability to diminish inflammation, reduce edema, and seal the blood–brain barrier, which decreases further influx of active immune-mediator cells and immunoglobulins (Ig) which lead to demyelination. Intravenous methylprednisolone can be followed by oral prednisolone for getting optimum results. Careful monitoring is required in order to keep the corticosteroid-induced adverse effects under control. Flushing, facial swelling, and a metallic taste in the mouth are such common side effects. Difficulty falling asleep and weight gain are other potential side effects of steroid usage in ADEM. Adrenal corticotrophic hormone (ACTH) has also been reported by many studies, to be effective in treating ADEM.

IVIG is generally administered, if steroids fail to control the disease. Some authors also say that IVIG is best used early in the course of the illness. IVIG

consists mostly of IgG molecules. For the treatment of ADEM, IVIG is used in a dose of 0.4 g/kg/day, for a period of 5 days. It has the same risks as any blood product, like allergic reactions and infection. Side effects also include headache, muscle pain, fever, and rarely aseptic meningitis. It also occasionally causes shortness of breath because of fluid overload. IVIG can also be very costly. There have been indications based on some studies that IVIG is preferable over plasma exchange in cases of postvaccination encephalomyelitis, but this is not substantiated yet. IVIG also leads to lesser incidences of relapse in ADEM and is very useful in the early part of the disease.

If this option fails, plasmapheresis or plasma exchange can be attempted, or drugs like cyclophosphamide and mitoxantrone can also be tried (Anilkumar et al. 2021). Antibiotics like minocycline are also useful, especially, in cases of ADEM after scrub typhus. This retrospectively hints at a plausible microbial link in ADEM. Plasmapheresis or plasma exchange for 5–6 times may be of help, too. Some reports suggest that IVIG may be more beneficial in patients with peripheral nervous system involvement, and plasma exchange is more effective in patients with demyelination associated with edema or swelling. However, plasmapheresis or plasma exchange should not be carried out in ADEM patients with autonomic dysfunction and hypotension. Side effects of plasma exchange include infection which is typically related to the need for an indwelling catheter, alteration of electrolyte profiles, and loss of coagulation factors.

Methylprednisolone along with IVIG has been successfully used in patients having atypical features of ADEM. Male sex, early initiation of therapy, and preserved reflexes can produce favorable outcomes in all modes of treatment (Murthy 2002). In severe cases of ADEM, and especially AHLE, cerebral edema can be seen. It should be managed with a combination of mannitol and hyperventilation. If these conservative approaches fail, then more drastic measures such as craniotomy are required (Bennetto and Scolding 2004). Hypothermia can also be used successfully in patients having fulminant ADEM (Alexander and Murthy 2011).

In the case of ADEM occurring after *Mycoplasma pneumoniae* infection, a combination of azithromycin and plasmapheresis produce a better clinical response than corticosteroids. Glatiramer acetate was earlier used for ADEM but is now used more commonly in MS. This molecule consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. It resembles myelin tissue or specifically MBP and, hence, has some immunomodulatory or inhibitory effect on the APCs which target myelin. In cases of ADEM occurring after pulmonary or CNS tuberculosis, four-pronged therapy with isoniazid, pyrazinamide, rifampicin, and ethambutol should be started rapidly along with corticosteroids for good results.

11.10.1 Probiotics as a Potential Therapeutic Option

After elucidating the role of the microbiome–gut–brain axis in demyelinating CNS diseases, there is increasing interest in manipulating the gut microbiota as a promising treatment option for these disorders. Probiotics are live microorganisms that benefit the host and are widely used in the treatment of enteric illnesses. The administration of probiotics may alter the microbiome functions and host interaction by increasing the population of a specific microorganism. Experimental and human studies show that probiotic agents may alter, reverse, or prevent various conditions like stress and anxiety, depression, social behavior, and cognitive functions. Fecal microbiota transplantation (FMT) is another new experimental approach that involves the reconstitution of microbes in gut with healthy microorganisms (Esmaeil Amini et al. 2020).

At present, there is no approved treatment option for ADEM or MS using gut microbiome manipulation. Many preclinical studies have shown good results in this context. Therapeutic manipulation of the gut microbiota could be a promising treatment option for many autoimmune CNS disorders (Calvo-Barreiro et al. 2018). Although there are no clinical studies available which show the benefits of probiotics therapy in ADEM, one recent study has shown an improvement in symptoms and quality of life in patients with MS after *L. reuteri* therapy (Kouchaki et al. 2017). Probiotic therapy has shown to be a potential component of treatment regimens which are used in autoimmune diseases. However, further studies are warranted to choose the optimal probiotic strains for this purpose.

11.10.2 Prognosis

During the clinical recovery phase of ADEM, MRI can still show worsening, thus showing a lag between clinical symptoms and MRI abnormalities. ADEM can generally have a more severe initial course, but also has reasonably better ultimate recovery than MS. The clinical outcome of ADEM, however, is also related to the antecedent factors. ADEM occurring after measles infection is associated with significant mortality (about 40%) and morbidity (60%). The mortality of post-varicella-zoster ADEM is about 10% and the morbidity is about 25%. The prognosis of acute cerebellar ataxia seen after VZV infection is very good. ADEM-related mortality in adult patients is about 8–25%, while in children, it is usually lesser than 5%. Hence, mortality is seen more in adults.

A small proportion of individuals who are initially diagnosed with ADEM can later on develop MS. Currently there is no method or known risk factors to predict whom those individuals may turn out to be (Bennetto and Scolding 2004). Nonresponsiveness to steroids is a known poor prognostic marker (Alexander and Murthy 2011). The presence of myelopathy, mean number of hours of altered sensorium, and the mean duration of hospital stay are usually associated with bad clinical prognosis. Fever at the time of admission, presence of ventilator-associated pneumonia, deeply altered sensorium at the nadir of disease, signs of meningeal

irritation at time of presentation, and lower motor neuron involvement during the disease are also associated with an immediate bad outcome (Iype et al. 2017). The presence of seizures is also a marker of poor prognosis. For most patients with ADEM, recovery begins within days. The majority of ADEM cases have total or almost total recovery within 6 months. In some cases, full recovery may take 6 months to 1 year or even longer.

11.10.3 Sequelae

The most common sequelae observed in patients after ADEM are focal motor deficits which can range from mild ataxia to frank hemiparesis. Psychiatric manifestations may also persist for a length of time. AHLE usually has a very poor prognosis overall. Sometimes the illness can assume a multiphasic characteristic. Chronic sequelae can also develop rarely. A detailed neuropsychological evaluation is hence recommended in order to assess possible neurocognitive defects that may arise and persist (Miranda and Ramos 2010).

11.10.4 Prevention

Acute intermittent porphyria or AIP can sometimes precipitate ADEM. In these cases, preventive measures like dietary control, abstinence from smoking and alcoholism are important to prevent an attack of ADEM.

11.11 Conclusion

It can thus be summarized that many different types of microorganisms can initiate as well as precipitate many demyelinating autoimmune diseases including ADEM. Autoimmune diseases like diabetes mellitus, psoriasis, systemic lupus erythematosus, as well as GBS, MS, and ADEM can thus all have possible or established microbial etiology behind them. Bacteria, fungi, viruses, parasites all can be responsible for these diseases. Sometimes, unlikely pathogens like *M. tuberculosis* or *Legionella* spp. can also be the cause, and sometimes, vaccination can be the precipitating event. Hence, a detailed history of infection or vaccination should always be sought for optimum management. A complex interplay of the host genotype, host microbiota, environment, diet, and microbial etiology can help in developing these autoimmune diseases like ADEM. More further research are hence desired in these aspects. This can open up new avenues of diagnostics and therapeutics. Microbiologists and immunologists can hence work in tandem for more fruitful research in this very interesting field.

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Part IV

Microorganisms in Pathogenesis and Management of Inflammatory Bowel Diseases (IBDs)

Microorganisms in Pathogenesis and Management of Ulcerative Colitis (UC)

12

Sanjiv Singh, Punita Aggarwal, Satyam Sharma, and V. Ravichandiran

Abstract

With the global rise in incidences of ulcerative colitis and various dysbiosis in the gut microbiota, there has been a growing demand to understand the development and cause behind this disease. Numerous findings have been predicted that gut microbiome is involved in the development of the ulcerative colitis and could also delay the healing process. Studies suggest that the penetration of gut bacteria inside the intestinal wall cause the release of interferon gamma, tumor necrotic factors, interleukins-1 and 6 (IFN-γ, TNF-α, IL-1, and IL-6) that produce reactive oxygen species which further damages the intestinal lining and at the top delays the healing process. The major role is played by the regulatory T cells (Tregs) and the formation of interleukin-10 (IL-10) via GPR43. The Treg cells are stimulated by IL-10 that causes activation of macrophages. Many pro-inflammatory mediators such as Th-1 and Th-17 are produced in response to invasive gut microorganisms (e.g., TNF-α, IFN-γ) by enhancing the transcription of significant genes. This chapter focuses on all the alternative pathophysiology and pathogenesis and management related to ulcerative colitis.

Keywords

Ulcerative colitis · Epithelial restitution · Intestinal wound healing · Pathophysiology · *H. pylori* · *Mycobacterium avium* complex · TNF-α · Treg cells

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12.1 Introduction

Ulcerative colitis is a very common inflammatory disease (long lasting); it is characterized by non-infectious inflammation that affects the colon and rectum. The condition is characterized by continuous inflammation that causes deep ulcerations on the rectum. Several factors can elicit ulcerative colitis—gut bacteria, immune system, genetic factors, and eating habits. The pathogenesis of ulcerative colitis is not very clearly understood, but new techniques and research over the intestinal microbiota have revealed a lot of information (Shen et al. 2018; Ohkusa and Koido 2015; Thoreson and Cullen 2007). To take a deep dive into this topic, we tried to get all the recent data and clinical trials to come up with a solid conclusion. Ulcerative colitis comes under the umbrella of inflammatory disease—chronic condition, idiopathy inflammatory disease. With all the latest research and data, it is quite clear that thickness of mucus and any alteration in its composition cause stress and can misfold the mucus associated with the protein. Any irregularities in the immune response involving the innate as well as the adaptive immunity can cause macroscopic lesions (Ordás et al. 2012; Keshteli et al. 2019). Ulcerative colitis can be characterized by the presence of pANCA (primary sclerosing cholangitis) antibodies and the isoform of 1 and 5 human tropomyosin or a bloody diarrhea. That include mycobacterium avium complex or its subspecies paratuberculosis aka MAP (Fries and Comunale 2011).

Other factors that play the major roles are diet and sucrose intake which maximize the risk of ulcerative colitis (UC). However, a diet rich in PUFA (polyunsaturated fatty acids) and vitamins/minerals has shown to surely reduce the chance of ulcerative colitis. Various reasonable theories for the etiology of gastrointestinal microbiota, microbiota metabolites formation, immune system changes, and gastric mucosal integrity have also been postulated (Kapel 1950; Gitter et al. 2001). The local complication of ulcerative colitis is colon cancer, rupture of the bowel, and massive hemorrhage. Many studies have confirmed that any inflammation can happen due to misfunctioning of M-cellsM-cells can causes antigen sampling that further lead to translocation of microbial peptide. Microbial peptide then further stimulate the immune cells to release interferon gamma, tumor necrotic factors, interleukins-1 and 6 (IFN-γ, TNF-α, IL-1 & IL-6), which produces reactive oxygen species, that involved in the ill effect of ulcerative colitisUlcerative colitis (UC) (Fig. 12.1) (Kevans et al. 2016; Martinez et al. 2008). The products of anaerobic respiration are thought to be produced by reactive oxygen species. In the course of interaction between the colon/rectum and the pathogen, the inflammation is limited to the mucosa and submucosa levels only. Neutrophils accumulated can be found infiltrating the crypts, forming crypt abscesses, and also the accumulation of phagocytes in the lamina propria, most notably neutrophilic granulocytes, which upon activation release large quantities of reactive oxygen species (ROS) that are cytotoxic to the mucosal cells as well as epithelial cells (Zhang et al. 2017; Nemoto et al. 2012; Angelberger et al. 2013). These compounds could be utilized by

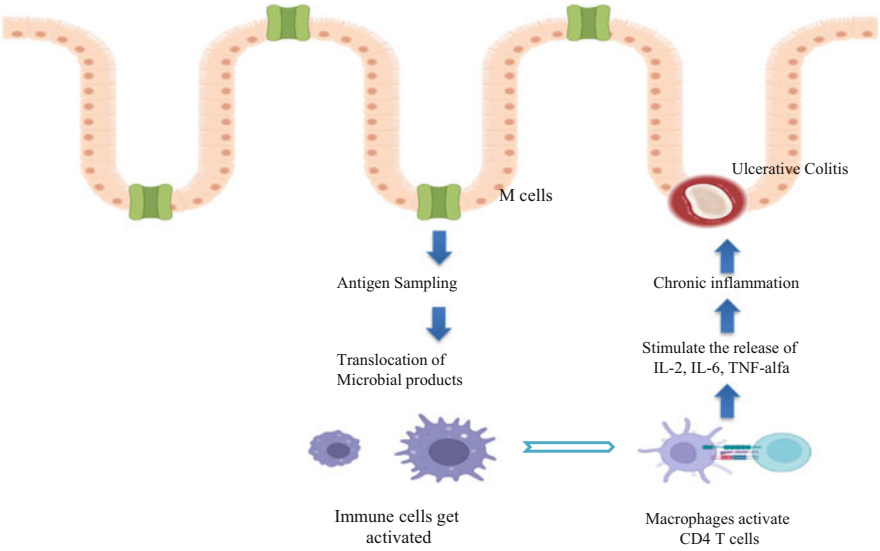

Fig. 12.1 Role of antigen (microorganism) in cytokine production in UC

facultative anaerobes to overrun, resulting in microbial populations being reduced. This dysbiosis microbiome could promote the formation of fungus which aggravate inflammatory response by activating the type-I T helper (TH1) pathway through chitin and glucan antigen-presenting cells (APCs). In addition, microorganism dysbiosis has been linked to an increase in bacteriophage species and activity, which can affect the overall microbiome through elevated levels of dimethyl sulfoxide, tetramethyl ammonium oxalate, and trimethylamine N-oxide (Sun et al. 2016; Paramsothy et al. 2019).

Potential significance of short-chain fatty acids (SCFAs) produced from fiber in maintaining gut microflora has been established, and SCFA acts as an energy source for intestinal mucosa. In addition, SCFAs also control the functioning of the gut wall as well as the immune response by signaling through G-protein-coupled receptors (GPCRs). Through the GPR43 receptor, SCFAs induce the development of regulatory T cells (Treg), stimulating the formation of cytokines (IL)-10. In addition, SCFA also stimulate IL-18 synthesis, which is important for anti-inflammation as well as epithelium healing, by facilitating upregulation in intestinal cells via GPR43. SCFAs potentially influence the functioning of the gut wall by inducing the expression of adhesion molecules as well as promoting the mucin production (MUC2) (Byndloss et al. 2019; De Leon et al. 2013; Bjerrum et al. 2010). The systemic complications that are caused by the ulcerative colitis are conjunctivitis, mouth ulcer, fatty liver, large joint arthritis, venous thrombosis, etc.

12.2 Role of Microorganism in the Pathophysiology of Ulcerative Colitis

Bacteria in the gut are more than important as ever, based on our limited diet we get. The intestinal lining especially of colon and rectum need to regenerate more quickly than any other cells or tissues in our body; the gut bacteria will produce different amino acid vitamins and proteins that will help repair these intestinal linings. The gastrointestinal microbiome plays an important mechanism in strengthening the gut immunity as along the way it also stimulates the lymphocytes for the expansion of colon, and it also prevents lymphocyte apoptosis. Studies show that with the lack of these bacteria in the intestine, the healing process is strongly hampered, which will further cause ulcer or inflammation to enhance (Fig. 12.2).

Some bacteria will selectively stimulate interleukin-12 productions like the Gram-positive bacteria, whereas some will induce interleukin-4 production like the Gram-negative bacteria (Marteau et al. 2004; Hendrickson et al. 2002). Mostly in small intestinal samples from patient populations with ulcerative colitis, Gram-negative anaerobic bacteria, particularly *Escherichia coli* and *Fusobacterium varium*, also with the existence of *Peptostreptococcus* encroachment, the

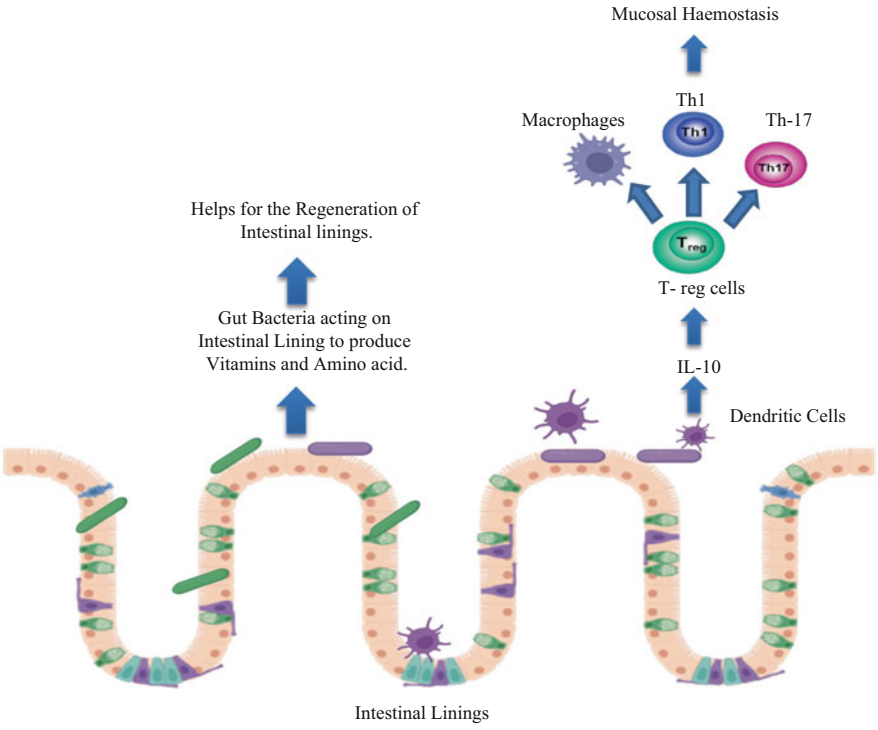

Fig. 12.2 Representation of action of gut bacteria on the intestinal linings. A healthy microbiota can help with immune tolerance and also cause mucosal hemostasis

possibilities of inflammatory response would also significantly raise, and so will drastic microorganism invasions of the mucous membranes, in contrast to healthy individuals (Macfarlane et al. 2004; Tamboli et al. 2004; Ohkusa et al. 2002). The relationships between respiratory epithelium as well as native microbial species (flora) are the focus of the emerging techniques. A few of them can now be used to identify ulcerative colitis from other conditions (e.g., anti-*Peptostreptococcus anaerobius* Ab-antibody) as well as colitis (e.g., anti I2-from *Pseudomonas fluorescens* antibody or antibody to an outer membrane porin of *E. coli*—anti-ompC) (Martinez et al. 2008). The bacterium composition of a gut activates epithelium and lymphatic tissues inside the gastrointestinal among both systemic and local immune function. MAP is eliminated from the feces of sick animals and released in their milk. Thus, there are two ways for MAP to cause infection: fecal contamination transfer via contaminated water and intake of infected breastmilk or items manufactured from contaminated milk (Head and Jurenka 2003; Hindryckx et al. 2016; Bjerrum et al. 2010).

One other possible way of inflammation and an early onset of ulcerative colitis is through the impairment of metabolism of epithelial cells (Borruel et al. 2002). The way it happens is that the anaerobic bacteria by the fermentation process ingest the carbohydrates and proteins to a SCFA which acts as a main source of energy for them. This fatty acid also works as an energy source for intestinal cells, and any variation in this energy can cause ulcerative colitis. The bacteria *Desulfovibrio desulfuricans* can cause an excess of hydrogen sulfide that acts as a toxin and leads to ulcerative colitis (Roediger 1980; Guo et al. 2020). Many RT-PCR assessments employing 16S rRNA-based species PCR primers revealed that *Rhodococcus erythropolis, Clostridium, Methanobrevibacter smithii, Desulfovibrio* (sulfate-reducing bacteria, SRB), Enterobacteria, type E *Clostridium perfringens*, *Enterococcus faecalis*, and enterohepatic *Helicobacter* species were substantially enhanced throughout UC (Frank et al. 2007) (Table 12.1).

1. ***Helicobacter pylori***: It is a common bacterium that can elicit ulcerative colitis. It is a Gram-negative microaerophilic bacteria with curved or spiral flagellated flagella. Although the mechanism is not clear, some consider it to be due to the immune regulation caused by *H. pylori.* Patients infected with *H. pylori* have higher levels of Foxp3, a T-cell regulatory marker that may help to prevent the progression of inflammatory bowel disease. A long-term infection of colon via the *H. pylori* causes partial or complete loss of parietal cells, and *H. pylori* has been detected in colon mucosa and the colonic tissues (Jin et al. 2013; Thomson et al. 2011).
2. ***Mycobacterium avium Complex***: MAP is indeed a pathogen discovered in the feces of animals. It infects and induces systemic infection in a broad range of animals, known as Johne's ("Yo-knees") disorder. Numerous systematic review and publication reviews had already indicated that the MAP species is consistently linked to Crohn's disease. A modest dosage of the MAP microorganism, or even many microorganisms infected a person at every given age, causes Crohn's

Table 12.1 Studies of microbiota in the pathophysiology of the ulcerative colitis

Sr. No.	Nonessential microorganisms	Role in pathophysiology	Study observed on	References
1.	*Helicobacter pylori*	Initiation of inflammation	Human	Jin et al. (2013), Bohr et al. (2004)
2.	*Clostridium difficile toxin/ Clostridium difficile*	Causes disease exacerbation	Human	Rhodes (1996)
3.	*Campylobacter concisus*	Initiate inflammation	Human	Jess et al. (2011), Gradel et al. (2009)
4.	*Fusobacterium varium*	Acts as pro-inflammatory, produces high concentrations of butyric acid, causing intestinal lesions	Human	Ohkusa et al. (2003, 2005, 2010)
5.	*Enterohepatic helicobacter*	Pro-inflammatory	Humans	Bohr et al. (2004)
6.	*Campylobacter* spp.	Initiate inflammation, also acts as pro-inflammatory	Humans	Jess et al. (2011), Kalischuk et al. (2009)
7.	*Campylobacter jejuni*	Initiates inflammation, also acts as pro-inflammatory	Humans	Jess et al. (2011)
8.	*Mycobacterium avium complex*	Initiate inflammation	Human	Pierce (2010)
9.	*Shigella* spp.	Initiate inflammation	Human	Gradel et al. (2009), Ternhag et al. (2008)
10.	*Salmonella* spp.	Diminished protective activity of the mucus, initiate inflammation	Humans	Rhodes (1996), Ternhag et al. (2008)
11.	*Yersinia* spp.	Initiate inflammation and produce toxic mediators	Human	de Oliveira et al. (2017)

disease, whereas a large dose of MAP causes ulcerative colitis (Pierce 2010; Bibiloni et al. 2006; Ohkusa and Koido 2015).

3. ***Fusobacterium varium***: One of the findings has suggested that diagnostic accuracy and ELISA titer of antibody against *F. varium* was dramatically higher in individuals having active UC than other individuals or control in a cohort study which comprised patients had active UC, CD, ischemic colitis, colonic adenocarcinomas, and normal individuals. Furthermore, individuals with UC had considerably greater immunohistochemistry identification for *F. varium* throughout the intestinal mucosa than some other participants. Furthermore, in vivo investigations revealed that *F. varium* is responsible for generating extremely high levels of butyric acid that induces gastrointestinal ulcers in animals that are comparable to those seen in UC patients (Ohkusa et al. 2003).

12.3 Role of Microorganisms in the Management of Ulcerative Colitis

Human gut is the home for millions of bacteria. Some of these bacteria that live in the colon and rectum in the pH from 5 to 7 are *Bacteroides, Clostridium, Streptococcus, Enterococcus, γ-Proteobacteria, Lactobacillus, Fusobacteria, Eubacterium*, and *Peptostreptococcus*. The microbiota in the gut helps with the immuno-modulation of both innate and adaptive immunity. The cell types like effectors Treg cells (T regulatory), IgA-forming B cells, group 3 innate lymphoid cells, dendritic cells, and the lamina propria all help in the immune modulatory function. Pathogenic microbiome drives the development of pro-inflammatory mediators (e.g., TNF-α, IFN-γ) via upregulation of key genetic sequences; when nonpathogenic bacteria invade intestinal mucosal wall of normal individuals, cells of the immune system generate regulating mediators (e.g., transforming growth factor as well as IL-10). It should really be noted how certain bacterial species inhibit the generation of proinflammatory mediators as well as cause stimulated macrophages eventually die via apoptotic mechanism (Borruel et al. 2002).

Their important function is to help with the synthesis of Vitamin- K as well as numerous vitamin-B substances that have key metabolic roles inside the intestinal flora, also they help to produce acetate, propionate, and butyrate. Butyrate emerges as a crucial power source for mammalian enterocytes, may trigger death in carcinoma cells, and can stimulate colonic glucose production, all of which shows the benefit on glucose and caloric expenditure. Because butyrate is needed by epithelium to utilize substantial O_2 via oxidative mechanism, ischemia occurs, which promotes oxygenation homeostasis inside the intestines and prevents gut microbial dysbiosis. It has been demonstrated that some microbial members of *Bacteroides* species conjugated linoleic acid (CLA) may be synthesized that helps with antidiabetic, antiatherogenic, antiobesogenic, hypocholesterolemic, and immune-modulating characteristics (Devillard et al. 2009; Sepehri et al. 2007).

Around 99% of intestinal microbiome comprises of four phyla—*Actinobacteria, Bacteroidetes, Firmicutes*, and *Proteobacteria* (Li et al. 2015). The anatomy of mucus layer has Muc2 as a polymeric sheet along with goblet cells that secretes bioactive molecules. The mucus layer of inner colonic is different from intestinal epithelial cells, and the bacteria in this reason do not trigger immune response. Although the inner mucus layer is not sterile and can come in contact of few bacteria, prolonged bacterial exposure has been associated with harmful immunological response, which could also misbalance MUC2 production as well as the features and function of the innermost mucous membrane (Bhinder et al. 2014). It has been seen that in case of ulcerative colitis, the thickness of mucus layer often decreases that makes it easy for the bacteria to reach epithelium and create an immune response.

An outermost layer is substantially highly elastic and has a greater amount than the internal lining due to proteolytic processing of Muc2 mucin. It produces large amount of mucin and mostly bacteria colonize around them. Thus, trails and studies have proven that Muc2 mucin helps build a mucous barrier/layer that prevent the

entry of bacteria into the colon epithelium, and any abnormalities in mucus wall can lead to the ulcerative colitis. Furthermore, numerous research studies focused on mouse ulcerative animals, including animals lacking Muc2 mucin as well as IL-10, which were immunostained to evaluate the Muc2 production throughout dextran sodium sulfate-treated animals. Microbial location in such mammal mucous was investigated, both bacterium and beads seemed to permeate the innermost mucous membrane. Any imbalance in the dysbiosis of gut and the bacterial clearance cause inflammatory response and can lead to ulcerative colitis (Swidsinski et al. 2005; Mayer 2000; Guarner and Malagelada 2003). Studies have shown that there is a decrease in Bacteroidetes and Firmicutes, while Proteobacteria and Actinobacteria increases in the mucosal inflammation (Li et al. 2015). Patients with ulcerative colitis have also shown reduction in *Butyricicoccus* bacteria in the gut, and the oral administration of *B. pullicaecorum* improved the morphological as well as histopathological measures. The study also reported health benefits as well as lower rates of intestine myeloperoxidase (MPO) and inflammatory cytokines (IL-12, TNF-α) levels. Moreover, in a Caco-2 cell line, supernatant generated from *Butyricicoccus pullicaecorum* cultures reduced the reduction of intestinal epithelial resistivity (TER) and enhanced IL-8 production generated with TNF-α as well as IFN γ (Eeckhaut et al. 2013) (Table 12.2).

Table 12.2 Studies of microbiota in the management of the ulcerative colitis

Sr. No.	Essential microorganisms	Effects	Study observed on	References
1.	*Lactobacillus acidophilus*	Anti-inflammatory, increases IL-10 levels	On mouse model	Bullock et al. (2004), Barroso et al. (2021)
2.	*Bifidobacterium bifidum*	Interacts with TLR-2 and facilities T-reg cell conversion	Human	De Kivit et al. (2014)
3.	*Escherichia coli*	Pro-inflammatory	Randomized human trails	Kotlowski et al. (2007), Sepehri et al. (2011)
4.	*Desulfovibrio desulfuricans*	Sulfate-reducing bacteria	Human	Roediger (1980)
5.	*Faecalibacterium prausnitzii*	Anti-inflammatory	Human	Lepage et al. (2011)
6.	*Pediococcus acidilactici*	Anti-inflammatory	Human	Nadal et al. (2009)
7.	*Lactobacillus salivarius*	Anti-inflammatory	Human	Fyderek et al. (2009)
8.	*Lactobacillus manihotivorans*	Anti-inflammatory and reduce thickness of mucus layer	Human	Fyderek et al. (2009)
9.	*Lactobacillus rhamnosus*	Suppresses NF-κB activation and prevents pro-inflammatory cytokine productions	Human	De Kivit et al. (2014)

1. **Bifidobacterial species**: Among 30 species, *Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium lactis, Bifidobacterium breve,* as well as *Bifidobacterium adolescents* act as a good source of energy in the gut. These bacteria synthesize the short-chain fatty acid, e.g., propionate and acetate which is further utilized by the intestinal cells to produce energy. Also, the *Bifidobacterium* species helps with the metabolism of oxalate that prevents the formation of kidney stones (Macfarlane and Macfarlane 2003; Sidhu et al. 1998).
2. ***Escherichia coli***: *Escherichia coli* is frequently located in the lower human as well as mammalian gut. Whenever *E. coli* colonizes at the larger intestinal of humans, this could improve digestion, nutritional processing, and uptake, as well as vitamin K synthesis. The mode of action and the nonpathogenic *E. coli* strain hypothesized throughout this research have been trying to block receptor sites to stop the establishment of adhesive microbes, antagonistic activity against pathogenic and nonpathogenic enterobacteria, most likely through the development of therapeutic drugs, and changes inside the pH as well as variable components of both the small intestinal lumen (Kotlowski et al. 2007; Sha et al. 2013). Studies also show that a random increase in the *E. coli* population might result in greater adherence scores than harmful *E. coli* colonies from normal subjects (Verma et al. 2010).
3. ***Lactobacillus* species**: *Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus paracasei, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus salivarius,* and *Lactobacillus helveticus* are the advantageous *Lactobacillus* genera. *Lactobacillus* is a Gram-positive, facultative anaerobic, rod-shaped bacterium. These lactic acid bacteria are involved in lactase synthesis, e.g., *Lactobacillus plantarum* (Mann and Li 2014). *Bifidobacterium* and *Lactobacillus* strains interact with TLR2 and/or TLR9 to both improve the functioning of the gastrointestinal epithelial layer and enable Treg cell conversions through $CD103^{+}$ DCs (Mann and Li 2014).
4. ***Faecalibacterium prausnitzii:*** These bacteria are found to have the anti-inflammatory properties. These bacteria produce butyrate which is indeed a main energy source for them and can activate intestinal gluconeogenesis. In fecal microbiota of the ulcerative colitis patients, there is a reduced number of *F. prausnitzii*. It is essential to maintain the population of *F. prausnitzii* for a healthy gut (Machiels et al. 2014).

12.4 Conclusion

With all the above study and data, we can easily predict that the microbiota plays a very crucial role when it comes to the development and repair of the gut and the health of our immunity. Human immunity also has a significant impact on the activity of the intestinal wall. A wide range of bacteria in gut and their population are responsible for the normal functioning. We have studied different mechanisms

by which gut microbiota and its population difference can induce or heal the ulcerative colitis. Further research should focus to figure out the exact population difference or alteration of gut microbiota that can induce ulcerative colitis. Bacteria such as *Lactobacillus casei, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, Streptococcus salivarius* subsp. *thermophiles*, and probiotic *Escherichia coli* have been demonstrated to lower inflammatory response as well as maintain recovery in ulcerative colitis patients. The microbiota in the gut helps with the immuno-modulation of both innate and adaptive immunity. Several cell types such as effector T regulatory cells, IgA forming B cells, group 3 innate lymphoid cells, dendritic cells, and the lamina propria help in the immuno-modulatory functions. Pro-inflammatory mediators are produced by invasive intestinal bacteria. Several clinical trials have been conducted and have revealed a positive effect on healing and treatment of ulcerative colitis. As our knowledge and understanding about different gut microbiota grow, it will help us better analyze our current medicine prescribed and how and what can be done to help keep the balance between the gut microbiota. These advancements will lead to an improved probiotic therapy that will restore the condition at the earliest.

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Microorganisms in the Pathogenesis and Management of Crohn's Disease (CD)

13

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease. It is considered to affect any part of gastrointestinal tract, but it majorly affects ileum and colon. Previous studies suggest that the etiology of CD is multifactorial including environmental, genetic, and infectious factors. Numerous studies report a dysbiosis of intestinal microbiota due to an imbalance between harmful and beneficial bacteria and viruses. Studies have revealed the role of intestinal gut microbiota in the progression of CD. Hence, probiotics are used for the treatment of CD which are responsible for exhibiting health-promoting properties such as modulation of immune responses, inhibition of pathogenic bacteria for reducing inflammation in Crohn's disease. The aim of this chapter is to provide insights on the gut microbiota-mediated pathogenesis in CD patients. In addition, the chapter also summarizes studies revealing potential role of probiotics, prebiotics, and fecal microbiota transplantation (FMT) approach for the treatment of CD.

Keywords

Probiotics · Crohn's disease · Prebiotics · Inflammatory bowel disease (IBD) · Fecal microbiota transplantation (FMT)

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13.1 Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD). It is considered as a transmural granulomatous inflammation which can affect any part of gastrointestinal tract (GIT) but majorly affects ileum and colon (Thia et al. 2010). Although the exact cause behind CD occurrence is unknown, previous studies suggest that CD occurs due to inappropriate immune response to the gut microbes in a genetically susceptible host. The prevalence of CD has increased across the globe since the twenty-first century (Ng et al. 2017; Hammer et al. 2016; Molodecky et al. 2012; Rocchi et al. 2012). At the turn of the twenty-first century, the occurrence of CD has accelerated up to 0.5%, while it is continuing to rise in developing countries (Benchimol et al. 2009; Kaplan 2015). Etiological studies reveal that several factors such as immune responses, host genetics, environmental stimuli, and the gut microbiota are responsible for the pathogenesis of CD. Gut dysbiosis has been associated with CD, and the emerging expansion in past years with high-throughput sequencing technology has unveiled the role of microbiome in the development of CD. These findings have given more insights to the researchers on the functional mechanisms of the microbiome in the pathogenesis and therapeutics of CD.

Probiotics are defined as live microorganisms which when consumed lead to health benefits in the host. Moreover, they have been suggested to impart a positive effect in gastrointestinal diseases like diarrhea and difficile colitis. They have been suggested to inhibit the overgrowth of pathogenic bacteria responsible for CD (McFarland et al. 1994; Kirchhelle et al. 1996; Shanahan 2004). Several animal studies have depicted the effectiveness of probiotic treatment in patients with CD (Mao et al. 1996). Some studies, conducted on *E. coli* Nissle 1917, *S. boulardii*, and VSL#3 reported ameliorating effects on patients suffering from CD (Guslandi et al. 2000; Rembacken et al. 1999; Kruis et al. 1997).

The gut microbiota which consist of bacteria, viruses, and other microorganisms play an indispensable role in maintaining the health of the host. CD is among those inflammatory diseases which are closely related to the gut microbiome. This chapter discusses the role of microorganisms, gut microbiota in the pathogenesis of CD, as well as probiotic or microbiota-based therapies in the treatment of CD.

13.2 Role of Gut Microbiota in the Pathogenesis of Crohn's Disease

One of the major causative factors observed in patients with CD is microbial dysbiosis (Kostic et al. 2014). Although bowel inflammation may be a reason for the development of microbial imbalance, studies on CD patients demonstrated that increase in pathogenic microorganisms and decrease in normal commensal microbes also result in chronic inflammation in CD patients (Sartor 2008; Frank et al. 2007). Study by Gevers et al. (2014) reported that microbial samples from patients with CD demonstrated increase in *Pasteurellaceae*, *Veillonellaceae*, *Fusobacteriaceae,* and

Enterobacteriaceae, whereas depletion in microorganisms *Clostridiales*, *Bacteroidales*, and *Erysipelotrichales* (Gevers et al. 2014). Moreover, rectal and ileal mucosal samples also depicted increase in *Proteobacteria* such as *Fusobacteria*, *Veillonella*, *Haemophilus*, and *Escherichia coli* and decrease in *Firmicutes* such as *Faecalibacterium prausnitzii* (Gevers et al. 2014). Similarly, several studies have described a decrease in *Faecalibacterium prausnitzii*, whereas increase in mucosa associated *E. coli* in CD (Willing et al. 2010; Lopez-Siles et al. 2014).

Furthermore, another study reported an increase in pathogenic organisms like *E. coli*, *Mycobacterium*, and *Campylobacter* species whereas decrease in populations of *Firmicutes* and *Bacteroidetes* in CD patients (Chassaing and Darfeuille-Michaud 2011). CD patients upon comparison with the healthy controls exhibited greater portions of mucosal surface associated bacteria with higher invasion and adherence property (Swidsinski et al. 2009). Studies also suggest that gut microbial profiling of CD patients from ileal or ilealcolonic portions were different from the healthy subjects; on the contrary, gut microbial profiling from the colonic portion of CD patients was like that of the healthy control subjects (Baumgart et al. 2007; Willing et al. 2010; Lopez-Siles et al. 2014). However, as compared to stool microbiome alterations, these studies have focused on exploring the mucosa-associated microbiota changes in CD patients. The above-mentioned studies indicate that future studies on CD should be focused on the incorporation of mucosal microbiome sampling along with fecal sampling.

13.2.1 Microbe–Host Interactions in Crohn's Disease

There are more than 500–1000 different species forming an intestinal microbiota, especially the human GIT contains 10^{14} of microorganisms (Gill et al. 2006). The composition of intestinal microbiota varies greatly from one individual to another. Epidemiological studies on European and African children showed that fecal microbial composition is largely influenced by the geography, diet, and hygiene (De Filippo et al. 2010). A report on twins showed higher similarity within fecal bacterial species among twins as compared to the genetically unrelated couples sharing same dietary and environmental habits (Guarner 2005). In a study conducted on patients with CD depicted reduction in diversity of the fecal microbiome compared to the healthy subjects (Manichanh et al. 2006). Similar results were also observed in the monozygotic twins for CD (Dicksved et al. 2008). Moreover, a low bacterial load was seen in the inflamed regions of CD patients (Sepehri et al. 2007). A multicenter study on pediatric CD samples revealed a decrease in *Bacteroidales*, *Erysipelotrichales*, and *Clostridiales,* whereas an increase in bacteria such as *Veillonellaceae*, *Pasteurellaceae*, *Enterobacteriaceae,* and *Fusobacteriaceae* (Gevers et al. 2014). Thus, the study suggests that rectal mucosa-associated microbiome profiling could serve as a potential biomarker for diagnosis of CD.

13.2.2 Intestinal Permeability

One of the major causes behind the IBD and CD is intestinal barrier function. Patients with CD have been reported with significant increase in intestinal permeability (Jenkins et al. 1987; Pironi et al. 1990; Adenis et al. 1992; Wyatt et al. 1997). Patients with active CD also exhibited the increased permeability that decreased upon the induction of CD remission (Sanderson et al. 1987). In CD patients, an imbalance in intestinal microbiota has been observed with decrease in commensal microbiota and increase in mucosa-associated bacteria. A study involving 16S rDNA profiling depicted diversity in mucosa-associated bacteria in active CD patients compared to the healthy subjects (Ott et al. 2004). Several metagenomics reports also showed depletion with several species of *Firmicutes* and *Bacteroidetes* phyla in CD patients when compared with control (Mondot et al. 2011; Sokol et al. 2008a, b; Frank et al. 2007; Martinez-Medina et al. 2006). Studies suggest that decrease in the population of *Bacteroidetes* phylum could result in inflammation since bacteria of this phylum such as *Bacteroides fragilis* exhibited ameliorating effects in the *Helicobacter hepaticus*-induced mouse model of colitis (Mazmanian et al. 2008). However, in case of *Firmicutes* phylum, decrease in *Faecalibacterium prausnitzii* was observed in CD patients when compared with healthy subjects (Sokol et al. 2008a, b). A mouse model study showed anti-inflammatory effects upon administration of *F. Prausnitzii*, indicating that decrease in *F. prausnitzii* may lead to the intestinal inflammation in CD (Sokol et al. 2008a, b). A number of studies have reported an increased frequency of *Enterobacteriaceae* members, particularly *Escherichia coli* in CD patients (Darfeuille-Michaud et al. 1998, 2004; Swidsinski et al. 2002; Neut et al. 2002; Martin et al. 2004; Baumgart et al. 2007; Kotlowski et al. 2007; Conte et al. 2006; Mylonaki et al. 2005). Moreover, a study suggested for increase in the few mucolytic bacteria such as *Ruminococcus gnavus* and *Ruminococcus torques* in CD patients (Png et al. 2010). These studies suggest an evidential link between the gut microbiota and abnormal intestinal permeability in CD patients.

13.3 Microorganisms in the Pathogenesis of Crohn's Disease

Intestinal microbiota are always in continuous contact with the intestinal mucosal surface. Considering the persistent threat of opportunistic invaders and abundance proportions of enteric bacteria, it is necessary that host maintains homeostasis at the luminal surface of the intestinal microbiota (Fig. 13.1). This is achieved by a perfect integration of intestinal barrier and immunotolerance between intestinal microbiota and luminal antigens.

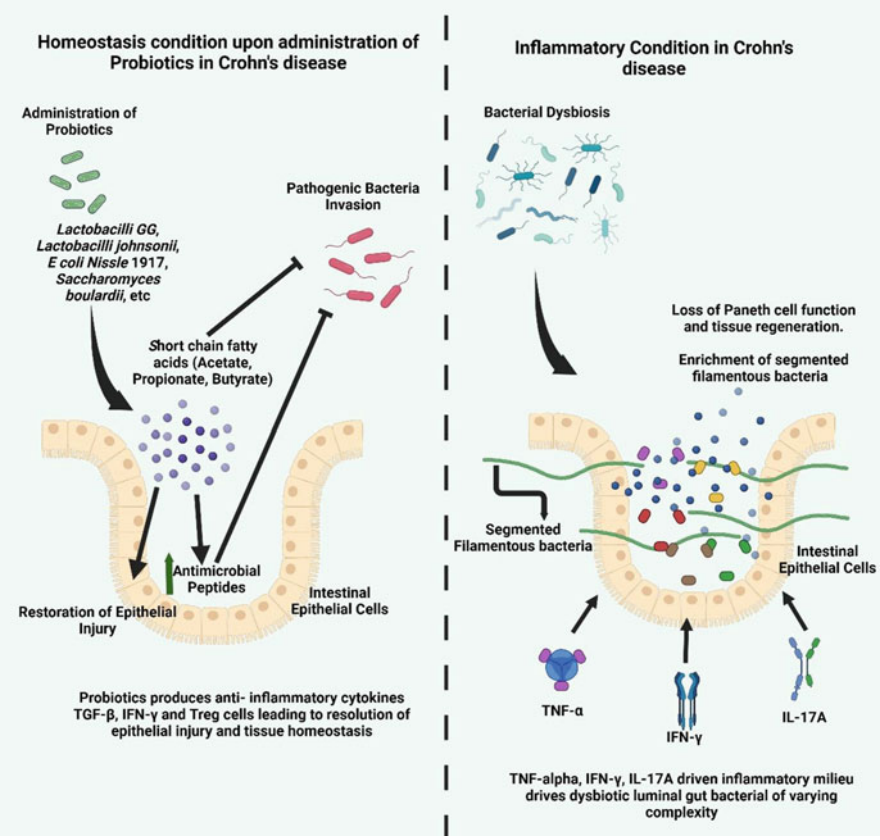

Fig. 13.1 Role of probiotics in maintaining host intestinal and microbial homeostasis in Crohn's disease. Under inflammatory condition, bacterial dysbiosis causes increase in segmented filamentous bacteria and other pathobionts. These microorganisms can breach the mucus barrier and interact with the inter-epithelial cells, which creates inflammation at local sites in a genetically susceptible host. Pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-17A cause dysbiosis in gut bacteria, thus results in the loss of Paneth cell function. The administration of probiotics such as *Lactobacilli GG*, *Lactobacillus johnsonii*, *E. coli* Nissle 1917 leads to inhibition of pathogenic bacteria through increase in antimicrobial peptide production via short-chain fatty acids (e.g., acetate, propionate, and butyrate) which ameliorate the inflammation. This finally leads to the resolution of epithelial injury and tissue homeostasis

13.3.1 Bacteria

Bacterial microbiota are among the well-studied part of the gut microbiota, which reside in host at variable concentrations. There is approximately 10^{11} or 10^{12} cells/g of luminal contents within the GI tract (Dave et al. 2012). There are 1000 bacterial species found in the human genome which contribute to a variety of crucial immunological and physiological functions of the host (Ley et al. 2006; Qin et al. 2010; Round and Mazmanian 2009). These functions include secretion of enzymes utilized

in performing metabolic processes and repression of pathogenic microorganisms (El Kaoutari et al. 2013; O'Hara and Shanahan 2006). Studies revealed that healthy gut microbiota inhabits *Actinobacteria*, *Verrucomicrobia*, *Bacteroidetes*, and *Firmicutes* predominantly (Jandhyala et al. 2015). The gut microbiota develop from less diverse community from birth to the more complex bacterial community from 9 to 12 months of age (Backhed et al. 2015; Koenig et al. 2011). The microbiota are hugely influenced by the dietary changes, antibiotic exposure, and environmental perturbations (Dethlefsen and Relman 2011; Wu et al. 2011). In addition, many other factors such as genetics, diet, drugs, and age are equally responsible for contributing to the gut microbial composition (Zuo et al. 2018; Maier et al. 2018; Yatsunenko et al. 2012).

According to a report, IBD patients harbor *Enterobacteriaceae* bacteria in abundance (Lupp et al. 2007). In another study, adherent-invasive *E. coli* was also found in the ileal CD biopsies (Darfeuille-Michaud et al. 2004). Overall, all these studies suggest that inflammatory environment in IBD and CD may result in excessive growth of *Enterobacteriaceae*. There are certain groups of gut bacteria which play an essential role in the prevention of CD. A wide range of microbial species such as *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus* have shown beneficial effects on the host through the stimulation of anti-inflammatory cytokines and downregulation of inflammatory cytokines (Sokol et al. 2008a, b; Llopis et al. 2009).

13.3.2 Viruses

With an increase in high-throughput sequencing technologies, it has been observed that gut virobiota have an indispensable role along with the gut microbiota in human host. Studies revealed that viruses contain diverse biological entities compared with the gut bacterial microbiota (Virgin 2014; Lecuit and Eloit 2013; Ogilvie and Jones 2015). The gut virome has an enormous number of bacteriophages, temperate single-stranded DNA *Microviridae* and double-stranded DNA *Caudovirales* which have the ability to infect host bacteria and kill other invading bacteria under stress conditions (Reyes et al. 2010; Minot et al. 2012; Waller et al. 2014).

There are ample amount of literature supporting the role of bacteriophages in the pathogenesis of IBD and CD (Perez-Brocal et al. 2015; Norman et al. 2015). CD patients exhibited higher range of diversity in gut virome as compared to the controls (Perez-Brocal et al. 2015). Another study on CD also suggested an increased virome, particularly bacteriophages from the *Caudovirales*, among the children suffered from CD (Wagner et al. 2013; Lepage et al. 2008). One of the major roles of enteric bacteriophages in IBD and CD may be the direct interaction with the mammalian host. In murine models, it has been indicated that bacteriophages have the ability to translocate from GI lumen to systemic sites and can also induce humoral immune responses (Górski et al. 2006; Uhr et al. 1962). Studies have proven the causal role of gut viruses in chronic GI inflammation in mice (Cadwell et al. 2010). For example, the gut norovirus infection led to the progression of inflammatory diseases such as CD (Cadwell et al. 2010).

In contrast to the above-mentioned studies, some viruses like norovirus have also shown beneficial effects on the intestinal abnormalities in germ-free (GF) mice and reduced the chances to intestinal damage caused via bacterial infection and chemical injury (Kernbauer et al. 2014). Moreover, viruses attached to mucosa can also provide protective measures against the epithelium associated bacterial invasion through Ig-like proteins exposed on the phage capsid and mucin glycoproteins on the mucosal surface (Barr et al. 2013). In a study on chemically induced colitis mouse model, the protective effect of gut virome was observed on the gut mucosal immune homeostasis (Yang et al. 2016). These findings have given more insights to the researchers on the role of gut virome in the pathogenesis and prevention of CD.

13.3.2.1 SARS-CoV-2

Novel RNA coronavirus also called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused COVID-19 pandemic (Chen et al. 2020; Huang et al. 2020). This virus is responsible for causing life-threatening acute respiratory distress syndrome (ARDS), pneumonia, and multiple organ failure and has emerged as a global health emergency (Chen et al. 2020; Huang et al. 2020). There is an urge to protect the health of people from COVID-19 and especially those individuals who are at high risk due to preexisting health conditions. Therefore, effective preventive measures and treatment strategies like vaccination is needed (El-Gabalawy et al. 2010). In case of IBD comprising CD and ulcerative colitis (UC), patients may need immunosuppressive medications such as corticosteroids, anti-cytokine treatments which includes anti-TNF and anti-IL-12p40 drugs, immunomodulators (methotrexate, calcineurin and thiopurines inhibitors, small-molecule inhibitors of signaling like tofacitinib), and anti-integrin therapies such as vedolizumab which can prevent susceptibility to SARS-CoV-2 infection within IBD, CD, and other immune-mediated inflammatory diseases (Jones et al. 2019; Ng et al. 2017; Kirchgesner et al. 2018; Lichtenstein et al. 2012). Health concern regarding the patients of immune-mediated diseases during the pandemic has led to the establishment of several health policies which includes shielding, i.e., physical distancing. So far, there are no solid evidence regarding the potential role of SARS-CoV-2 in the pathogenesis of CD, but there is risk associated with the increased susceptibility toward the viral infection.

13.4 Therapeutic Role of Microorganisms in the Management of Crohn's Disease

Emerging studies have influenced to gain more insights for the role of gut microbiota, on the host immune response, and aided in finding ways for manipulating and exploring the role of microbiota in modulating host immune response and restoring health (Fig. 13.1). Various studies have explored the potential role of gut microbial community with prebiotics and probiotics in patients with CD. These studies are summarized in the below sections.

13.4.1 Role of Prebiotics and Probiotics in the Treatment of Crohn's Disease

Prebiotics help in the growth and colonization of beneficial microorganisms within gut. Few commensal organisms produce short-chain fatty acids (SCFAs) upon fermentation of indigestible fibers, which provides crucial energy sources for intestinal microbiota. In several IBD studies, there was notable reduction within SCFA producers in CD which resulted in bacteria such as *Faecalibacterium*, *Phascolarctobacterium*, and *Roseburia* (Morgan et al. 2012). This study also reported decrease in genes involved in metabolism such as propanoate and butanoate in ileal CD. Despite the fact that the high diet fiber is associated with decreased risk of CD, there is no evidence in support of its role in the treatment of CD (Hou et al. 2011). One preliminary study suggests that fructo-oligosaccharide (FOS) upon fermentation normalizes the ileal commensal microbes (Barnes et al. 2012). A study on 10 patients with active ileocolonic CD exhibited significant decrease in disease activity and increase in fecal *Bifidobacteria* upon receiving 15 g of inulin regularly for 3 weeks (Lindsay et al. 2006). However, in another study, there was no clinical benefit observed in active CD patients upon administration of prebiotic fiber (Benjamin et al. 2011). Presently there is no solid evidence which could support the utilization of prebiotics in the treatment of active CD. Hence, further studies are needed to explore its role in CD therapy.

As mentioned above, the relationship between gut microbial dysbiosis and CD suggests that uptake of probiotic strains can help in providing balance of intestinal microbes leading to improvement of the disease activity. Various studies examine the role of probiotics in CD treatment and maintenance (Table 13.1). So far, probiotics studied for CD includes *Lactobacilli GG*, *Lactobacilli johnsonii*, *E. coli* Nissle 1917, and *Saccharomyces boulardii*. Few studies have also evaluated the combinatorial effects of prebiotics and probiotics in the treatment of CD. An open-label study on 10 patients with active CD patients upon administration of probiotic containing *Bifidobacterium breve*, *Bifidobacterium longum*, and *Lactobacillus casei* and a prebiotic (psyllium) reported improvement in symptoms of seven patients (Fujimori et al. 2007). Another study on 35 patients with CD upon receiving *B. longum* and inulin/oligofructose (growth substrate as prebiotic) showed significant improvement in 62% of CD patients (Steed et al. 2010). Similarly, a pilot study on four children with active CD demonstrated remarkable improvement on clinical aspects upon administration of *Lactobacillus GG* (10^{10} CFU/tablet, twice a day for 6 months) (Gupta et al. 2000). However, the low sample size and the absence of control in the study undermined the reliability of the study. Overall, at present, there is lack of data to support the efficiency of probiotics in the treatment of CD.

13.4.2 Fecal Microbiota Transplantation

Considering the potential aspects of intestinal microbiota in CD pathogenesis, recently another therapeutic approach has been considered for the treatment of CD

Table 13.1 Studies on fecal microbiota transplantation (FMT) and probiotics for the treatment of Crohn's disease

Therapeutic regimen	Number of patients	FMT route/probiotics administered	Findings of the study	References
One dose of 50 g of feces/ 250 ml of saline	19	Colonoscopy	58% of clinical response	Vaughn et al. (2016)
One dose of 150–200 ml	30	Endoscopy	86.7 and 76.7% of clinical improvement and remission at week 4	Cui et al. (2015)
One dose of 30 g of feces/ 100 or 200 ml of saline	9	Nasogastric tube	77.77% of clinical remission at 2nd week 55.55% clinical remission at 6th and 12th week	Suskind et al. (2015)
B. breve; *L. casei*; *B. longum*	10	Oral administration of 75×10^9 bacteria/day; once a day for 13 months	60% clinical remission & 70% of clinical responsiveness	Fujimori et al. (2007)
Lactobacillus GG	4	Oral administration of 10^{10} CFU/dose; twice a day for 6 months	75% of clinical improvement at 4th and 12th week	Gupta et al. (2000)

known as "fecal microbiota transplantation (FMT)." FMT has been shown to be effective in UC as in this therapy fecal microbiota are transferred from a healthy individual to the gut of a patient which enables the re-establishment of a normal microbial flora (Damman et al. 2012; Karadsheh and Sule 2013). However, very few studies and case reports of FMT have been reported for the management of CD. The first report was of a 31-year-old man with terminal ileal CD which remained symptom free for 4 months after the transplantation (Borody et al. 1989). Another study on FMT resulted in clinical remission of severe CD for the treatment of more than 9 months (Zhang et al. 2013). Study in IL-10 knockout mouse model showed decreased diversity and depletion in *Clostridia* and *Bacteroidia* (Perry et al. 2015). Post-surgery, there was decrease in microbial diversity with predominant expansion of *Proteobacteria* and *Firmicutes*. Moreover, microbiome analysis after FMT revealed a consistent decrease in diversity in the donor's stool. The sham-transplanted group of mice showed increase in microbial species such as *Staphylococcus*, *Lactobacillus*, *Enterococcus*, and *Streptococcus* compared to FMT and control groups. *Klebsiella* uniformly expanded within all the animals of FMT group despite the low relative abundance in the donor stool. Additionally, there was also an increase in bacteria such as *Parabacteroides*, *Alistipes*, and *Bacteroides* in FMT animals (Perry et al. 2015). Most of the evidences gained on the ameliorating effects of FMT in CD have been obtained from small and uncontrolled studies (Table 13.1). An FMT done by colonoscopy depicted improvement in patients

with 58% clinical outcome (Vaughn et al. 2016). This study also reported increased levels of regulatory T cells (Tregs) in patient's lamina propria with higher microbial diversity and less inflammation. Tregs have been reported to exert anti-inflammatory effects through the secretion of IL-10 and TGF-β cytokines (Dwivedi et al. 2016). Moreover, Tregs suppress the active inflammatory cells including Th1 cells (Dwivedi et al. 2016). In another study, single-dose treatment with FMT showed clinical improvement and remission based on clinical activity in CD patients (Cui et al. 2015). Suskind et al. also examined the beneficial role of FMT in nine young patients (12–19 years of age) with CD. Moreover, upon receiving FMT by nasogastric tube for 12 weeks, five patients showed remission of CD (Suskind et al. 2015). However, more studies with clinical trials and better standardized protocols for confirming ameliorating effects of FMT in CD are required.

13.5 Future Perspectives

Several efforts have been made till date to characterize the human gut microbiota in health and CD. Although bacterial microbiota are one of the most studied gut microbial components, their function and strain level resolution studies still need to be addressed. Moreover, it is also important to focus on the under-studied gut microbiota components like viruses and fungi, as they impact the health of CD patients. Overall, the future mechanistic studies are required for better understanding of the complexity of the gut ecosystem. In addition, the precise analysis of the cause of microbial alterations also requires integration of gene expression studies to explore the microbial-host interaction. Though the microbe-based therapeutics involving prebiotics, probiotics, and FMT are appealing and effective, these therapies require a personalized approach for the identification of patients and possible prognosis for the CD.

13.6 Conclusion

Patients with CD exhibit decreased microbial diversity, which is an important reason for pathogenesis of CD. A better knowledge is needed for understanding the host–microbe interactions in CD. Microbial restoration therapies are considered as an important alternative for the management of CD, and this may be utilized in developing a standardized and personalized therapy in the future. Targeted therapies such as dietary manipulation, prebiotics, probiotics, and FMT can be used for modifying the gut microbiota structure and function for the treatment of CD patients.

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Microorganisms in the Pathogenesis and Management of Pouchitis

14

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Abstract

Pouchitis is the most frequent clinical complication following restorative proctocolectomy with ileal pouch anastomosis surgery to treat inflammatory bowel diseases. It results in the inflammation of the pouch, and its etiological agents include altered immunological response, genetic factors, diet, and obesity. However, the role of microorganisms in the pathogenesis and management of pouchitis is gaining more attention as dysbiosis is frequently observed in pouchitis cases and most of the time treated with antibiotics. Moreover, several bacterial therapies are now emerging as a safe and effective alternative for pouchitis treatment and prevention from egress. Colonization of pathogenic microbes in the pouch leads to an increase in gut permeability, more synthesis of pro-inflammatory factors, a decrease in the production of short-chain fatty acids, and a reduction in helpful host–microbiome diversity. The mechanism of action of beneficial bacteria in pouchitis treatment involves inhibition of entry and colonization of pathogenic bacteria by lowering pH of the lumen, production of antimicrobial compounds, and blocking the binding of pathogens. It also includes improving pouch mucosal and epithelial properties as high integrity, more short-chain fatty acid, and immunoregulation with more immunoglobulins and elevated cytokines. Microbial interventions such as probiotics, microbial restoration

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therapy, and fecal microbiota transplantation have great potential to reduce, suppress pouch inflammation, and relapse of pouchitis after antibiotic treatment.

Keywords

Pouchitis · Inflammatory bowel diseases (IBDs) · Ulcerative colitis (UC) · Probiotics · Restorative proctocolectomy · Microbiota · VSL#3 · *Bifidobacterium* · *Lactobacillus*

14.1 Introduction

14.1.1 Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are a group of chronic relapsing intestinal disorders exemplified by ulcerative colitis (UC), Crohn's disease (CD), and familial adenomatous polyposis (FAP). IBD is a severe inflammation in the gastrointestinal tract and is proposed to be a predisposition factor leading to colorectal cancer (Ananthakrishnan et al. 2013). Globally there were around 6.8 million cases of IBD, according to the report of Global Burden of Disease (GBD) 2017. The prevalence rate is amplified from 79.5 per 100,000 population in 1990 to 84.3 per 100,000 population in 2017 (Alatab et al. 2020). In the United States alone, around 907,000 people have UC. Despite medical advancement in the treatment of IBD (antibiotics, immunomodulators, and biologicals), approximately 30% of UC patient undergoes surgery, experience treatment side effects, cancer, and at the end, after all, an option found to be less effective has to go for colectomy and ileal pouch-anal anastomosis (IPAA) (Szeto and Farraye 2017).

14.1.2 Basics of Pouchitis

A pouch is an artificial rectum created from a part of the ileum, and it is connected to the anus. Multiple pouch configurations (Kock pouch, J, S, W pouch) have been evolved over the years, and the selection of a particular pouch depends on indication of colectomy, technical feasibility, and mucosectomy. The J-pouch has become the most commonly used one due to ease of construction and efficiency of evacuation. The incorporation of pouch improves the health quality of patients and reduces the risk of IBD-associated colorectal cancer (Shen 2013).

Pouchitis is a prevalent complication in patients undergoing restorative proctocolectomy to treat UC, CD, and FAP (Lichtenstein et al. 2016). Around 23–46% of patients with UC who have received ileal pouchanal anastomosis (IPAA) subsequently develop pouchitis (Philpott 2017). Pouchitis, which is defined as the acute and/or chronic inflammation of the ileal reservoir, represents the most common long-term adverse sequel after IPAA (Shen 2013). Hence, pouchitis is not a single disease, but it is a continuum of disease including various diseases, and its

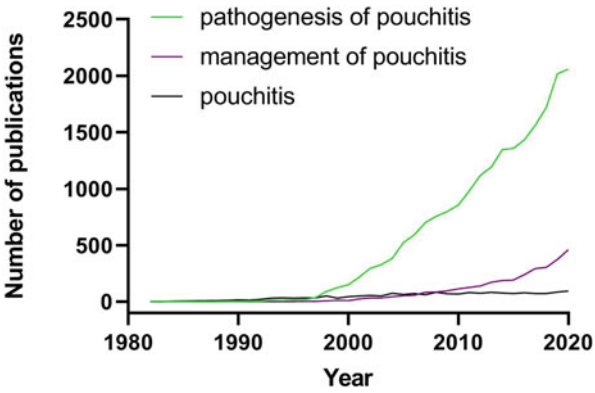

Fig. 14.1 Research publications related to pouchitis. Studies related to management (microbial) is very less as compared with pathogenesis of pouchitis

etiologic parameters and ways of pathogenesis. The severity of pouch inflammation is generally analyzed by pouch disease activity index (PDAI), which involves a study of clinical symptoms (0–6 points), endoscopic (0–6 points), and histological findings. A total point score > 7 is considered positive for pouchitis (Fazio et al. 2013). However, few studies reported PDAI as 19-point scale of pouchitis based on clinical, endoscopic, and histological analysis (Sandborn et al. 1994). There is a close similarity between UC, CD, and pouchitis, as in pouchitis similar to UC and CD, mucosal inflammation occurred in areas with the highest concentration of bacteria. Because of this similarity, pouchitis is sometimes considered the third form of IBD (McLaughlin et al. 2010).

Pouchitis results from inflammation in the pouch leading to abdominal cramping, rectal bleeding, rectal urgency, fever, and incontinence (Alatab et al. 2020). Pouchitis is classified as acute and chronic on the basis of reaction to antibiotic therapy. Symptoms of acute pouchitis persist less than 4 weeks and usually respond to the antibiotics treatment. At the same time, chronic pouchitis lasts longer despite antibiotic therapy and is also termed antibiotic-dependent and antibiotic-refractory pouchitis (Akiyama et al. 2021). On the basis of pathogenesis, pouchitis is classified into three main categories: (1) microbiota-associated pouchitis, (2) immune-mediated pouchitis (primary sclerosing cholangitis-associated pouchitis and IgG4-associated pouchitis), and (3) ischemia-associated pouchitis (Shen et al. 2008).

Currently available literature regarding pouchitis mainly focuses on pathologies and few studies focused on the role of microbes in inflammation and management of disease (Fig. 14.1). For the diagnosis of pouchitis, generally, three types of information are used: (1) characteristic symptoms (diarrhea, urgency, abdominal cramp, pelvic discomfort), (2) endoscopy (erythema, ulcer, bleeding), and (3) histology (crypt abscesses, inflammatory infiltrate) (Coffey et al. 2009). The treatment and prophylaxis of pouchitis involved the use of antibiotic therapy (ciprofloxacin, metronidazole, rifaximin, etc.), monoclonal antibodies (infliximab, adalimumab, vedolizumab, ustekinumab, etc.), and prebiotics (Geier et al. 2007; Chowdhry and Katz 2014). Healthy human microflora and probiotics are emerging microbial agents

for managing and treating acute and chronic pouchitis (Geier et al. 2007; Akiyama et al. 2021).

As the pouch is a surgically created new organ, its cellular, histological, and microbial composition is distinct from the native ileum. Reasons behind the development of pouchitis in still unclear but obesity, the role of the bacterial population, inappropriate immune response, genetic factors, and alteration of microflora were found to play important roles (Philpott 2017). Several risk factors for pouchitis include smoking, backwash ileitis, extra intestinal manifestations (EIMs), especially primary sclerosing cholangitis (PSC), elevated white blood cell count, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), mutations, and certain dietary factors (Chowdhry and Katz 2014; Gionchetti et al. 2021).

Multiple studies have shown that the occurrence and risk of pouchitis are highest during the first year after the IPAA surgery, and the incidence and risk levels decrease after the first year. The probability of pouchitis after 10 years of IPAA surgery is reported in the range of 23–60% (Penna et al. 1994). The frequency of pouchitis in patients with IPAA surgery for UC is significantly higher than that of patients with FAP. Nearly half of patients who undergo IPAA surgery for UC are diagnosed with at least one episode of pouchitis. On the other hand, in patients with FAP receiving the same IPAA, the occurrence of pouchitis is significantly less (0–11%). The above data suggest that the inflammation and pathogenesis in UC may play a significant role in the development of pouchitis (Szeto and Farraye 2017).

Microflora are significantly affected in UC pouch as compared to the FAP pouch. In UC-infected pouch, sulfate-reducing bacteria are abundant than in FAP pouch producing hydrogen sulfide as a byproduct of their metabolism. Hydrogen sulfide interferes with normal colonic metabolites and excavates mucosal injury (Singh and Lin 2015). Short-chain fatty acids (SCFA) are also found in low amounts in pouchitis feces as compared with fecal samples from a healthy pouch and FAP patient (Bath et al. 2011). The increase and decrease in prevalence may be due to distinct differences (environmental, cellular, and immunological) in UC pouchitis and FAP pouchitis.

14.2 Microorganisms in Pathogenesis of Pouchitis

Since evolution, humans and their microbiota have developed together to reach a state of equilibrium. The human gut microbiome is dominated by specific bacterial phyla, such as *Firmicutes* and *Bacteroides*, with smaller proportions of *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* (Chowdhry and Katz 2014). Dysbiosis is the disturbance in the richness and evenness of commensal communities relative to those found in healthy individuals. For example, reduced *Firmicutes* (*F. prausnitzii*) diversity was mainly observed in the gut microbiota of patients with IBD (Peterson et al. 2008). Several studies proved that a shift in microbial population within the pouch and original ileum is typical (Merrett 1997; Coffey et al. 2009; Hinata et al. 2012). The antibiotic use in the treatment of pouchitis provides plausibility of microbial influence in disease development.

Table 14.1 Major pathogens commonly associated with pouchitis and their role in disease progression

Sr. no.	Pathogens	Major findings for pathogenesis	References
1	*Bacteroidaceae* species, *Clostridiaceae*	Proinflammatory effects	Scarpa et al. (2011)
2	*Enterococcaceae*, *Enterobacteriaceae*, *Streptococcaceae* species	Homeostatic impact and reduce inflammatory events	Scarpa et al. (2011)
3	*Campylobacter, E coli,* and *Histoplasma capsulatum*	Cause infection in pouch	Shen (2013), McCurdy et al. (2013)
4	Cytomegalovirus (CMV)	Induce inflammatory response	Casadesus et al. (2007)
5	*Haemophilus* and *Streptococcus*	Disturb epithelial barrier integrity via protease	Hoffman et al. (2019)

Several microorganisms are involved in pathogenesis and progression of pouchitis (Table 14.1).

In the pouchitis, large amounts of *Fusobacter* and *Enterobacter* were observed with the concomitant absence of *Streptococcus* species in the infected pouch (Segal et al. 2018). Pouchitis has been shown to be associated with a decrease in *Lactobacilli* and *Bifidobacteria*, indicating that this disease may be the result of an unstable microflora (Ruseler-van Embden et al. 1994).

Most notably, pouchitis is reported to be associated with an increase in the population of anaerobic bacteria communities such as *Clostridium perfringens, C. coccoides*, *C. leptum, Bacteroides fragilis, Fusobacterium*, and *Atopobium* with a consecutive decrease in bacterial species commonly dominant in the ileum, including *Lactobacillus* (Hinata et al. 2012). A reduction of microbial diversity is considered to be an early sign of development in pouchitis. This shift in the microbiome is associated with some biochemical changes carried out by microbes, such as sulfate reduction, SCFA, and bile salt composition (Coffey et al. 2009). Altered microflora metabolites such as bile acid, volatile acid stimulate pouch inflammation, and a concomitant decrease in SCFA, butyric acid makes the pouch more susceptible to inflammation (Ruseler-van Embden et al. 1994). The SCFA maintains the epithelial barrier and immune response by IgA production (Sznurkowska et al. 2020). Study by Gosselink et al. (2004) reported that pouch microflora in the absence of inflammation contains *Lactobacilli*. Still, there is an increase in anaerobic bacteria during pouchitis development and a decrease in *Lactobacilli* with higher numbers in *Escherichia coli* (hemolytic strains). Metronidazole eliminated *C. perfringens*, while ciprofloxacin inhibited the growth of *C. perfringens* and hemolytic strains of *E. coli.* Furthermore, Reshef et al. (2015) conducted a microbial diversity analysis among 140 pouch patients, including 131 UC and 9 FAP. They found that the alpha diversity was similar among UC patients with and without a pouch and FAP patients with a pouch, but it was low in healthy pouch patients. A significant decrease in genera belonging to the

Lachnospiraceae, *Bacteroides*, *Collinsella*, and *Ruminococcaceae* families was also observed. Few reports pointed out the role of *Campylobacter, E. coli,* and *Histoplasma capsulatum* and cytomegalovirus (CMV) in causing infection in a pouch (Shen 2013; McCurdy et al. 2013). Association of CMV with pouchitis was majorly observed in immunocompromised patients and improved upon antiviral treatment (McCurdy et al. 2013). According to mPDAI (modified pouchitis disease activity index), CMV is commonly observed in pouchitis patients compared to those with typical pouch (Casadesus et al. 2007). There are three reasons for CMV pouchitis; CMV acts as a witness in pouch inflammation, may have some role in pouch inflammation after other pathogen attacks, and may induce an inflammatory response after infection (Casadesus et al. 2007).

14.3 Gut Microbiota Dysbiosis in Pouchitis

Gut microbiota and mucosal biofilm of the healthy human population is distinct, and shift in this gut microflora (dysbiosis) leads to the formation of protective (non-inflammatory) to hostile (pro-inflammatory) microbial communities. Such dysbiosis makes the patient more susceptible to pouch inflammation representing microbial stasis that occurs in the pouch and is absent in the ileum (Komanduri et al. 2007). Apart from dysbiosis-related stasis, high chance of disturbance in normal homeostasis (cross talk) between luminal bacteria and mucosa (biofilm) due to loss of protective biofilm is another reason, as this leads to an imbalance between anti-inflammatory and pro-inflammatory bacteria (Chichlowski and Hale 2008).

Ruminococcus gnavus (strictly anaerobic bacterium from human fecal microbiota) reported to produce an antibacterial compound "ruminococcin A." The ruminococcin A was very active against pathogenic *Clostridia* (Dabard et al. 2001). The absence of *R. gnavus* in infected pouch may allow inflammation by proinflammatory bacteria such as pathogenic *Clostridia*. Similarly, *Streptococci* species (part of VSL#3) is used to treat pouchitis because it acts as anti-inflammatory bacteria in the pouch. The presence of excessive proinflammatory bacteria (*Fusobacter* and *Enterobacter*) in pouchitis increases proinflammatory cytokines, leading to a further increase in disease magnitude via inflammation induced injuries (Hessle et al. 2005).

Ruseler-van Embden et al. (1994) did a meaningful study about how microbial imbalance results in pouch inflammation. They collected stool samples from patients with and without pouchitis and analyzed microbial diversity, pH difference, and mucus lytic potential. It was observed that flora of pouchitis has less *Bifidobacteria* and anaerobic *Lactobacilli* and a large amount of *Clostridium perfringens* (75% of total pouchitis samples). The pH of the pouchitis stool sample was notably high (6.5), while it was low (5.4) in a control stool sample. High pH can be considered a sign of microflora instability. Mucosal cells have a layer of mucus glycoproteins protecting against inflammation, mechanical injury, antigen and toxin attachment, and invasion by pathogens. In the intestine mucus produced by goblet cells also promotes antibacterial proteins such as lactoferrin and IgA. The loss of goblet cells

decreases mucus integrity and increases bacterial translocation, leading to a change in pro-inflammatory cytokines and T- cell profile (LeBlanc et al. 2021).

At higher pH, the protective mucus glycoprotein is removed by the glycosidase activity of altered microflora. Mucus degradation remains continued by the host proteolytic enzyme after initial damage by glycosidase. The pouch microflora degrades twofold more mucin at near neutral pH as compared with low pH. Mucin degradation also happens in a healthy pouch, but its secretion from goblet cells balances the degraded glycoprotein part of mucin. Most importantly, maintaining low pH in the healthy pouch by normal microflora metabolites inhibits or slows down the rate of mucin degradation. Bacterial antigens may activate the immune system due to the weakening of mucosa, and it also allows entry of host protease. High unconjugated bile acids have been present in the fecal pouchitis sample; anaerobic bacteria metabolize primary bile salt and release unconjugated bile acids. Unconjugated bile acids are harmful to the membrane and may predispose a typical pouch to inflame pouch (Nasmyth et al. 1989).

Mucin chemical composition is also related to pouchitis. Unique mucin profile was found in the normal rectum and colon biopsy specimen; however, a patient with UC was deficient with oligosaccharide side chain mucin species IV (as chances of pouchitis are higher in UC patients than in FAP). In remission, the colonic mucin sample of UC patients showed a decrease in mucin fraction III and an increase in fraction V compared with active UC (Podolsky and Isselbacher 1984). The change in the type of mucin in the inflammatory pouch from a high degree of sialylation to more sulfated (Corfield et al. 1992). A correlation can be made from pouch mucus change in UC, and subsequent development of pouchitis as mucus of UC patients may be more prone to degradation by pathogens glycosidase followed by host protease as compared with FAP, and this maybe the hidden reason why pouchitis prevalence is high in UC them FAP.

Hoffman et al. (2019) observed an increase in pouch inflammation and epithelial membrane disruption due to protease produced by *Haemophilus* and *Streptococcus.* Fecal analysis of pouchitis patients showed fivefold more protease than the typical pouch due to the above species being widely known for protease production. It was found that fecal sample supernatant after reaction with Caco-2 cell monolayer activated protease activating receptor on Caco-2 cell monolayer. This activation leads to the collapse of epithelial integrity leading to higher permeability and disruption in tight junction proteins. The present study's finding is relatively valid for patients suffering from UC and CD as dysbiosis in pouchitis has similarities with that of other IBD.

A separate study demonstrated that pouchitis flora stimulates human lymphocytes (peripheral blood mononuclear cells or lamina propria mononuclear cells) as compared with pouch flora without pouchitis. Treatment of metronidazole to pouchitis flora diminished their stimulatory ability (Bell et al. 2004). Individuals are generally tolerant to owning microflora and proliferating against foreign flora. The author indirectly proves the presence (rather than identification) of flora in the inflamed pouch. The present study provides another evidence of bacterial pathogenesis in earlier inflammation leading to activation of mononuclear cells.

All these consequences lead to the accumulation of toxins, free radicals, loss of colonization, and a decrease in the synthesis of SCFA. All of the above events stimulate pouchitis development by creating an inflammation prone environment (Ruseler-van Embden et al. 1994).

14.4 SARS-CoV2 and Pouchitis

Very few reports are currently available regarding correlation of pouchitis (IBD in general) and Coronavirus disease 2019 (COVID-19) other than palliative care guidelines (Dhar et al. 2020; Iacucci et al. 2020; Chela et al. 2021; Chebli et al. 2021). Immunocompromised individuals and comorbids are more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 (Chela et al. 2021). Sometimes immunosuppressive agents are used to treat IBD; hence, relatedness is expected during simultaneous treatment of COVID-19 and IBD. IBDs are also related to deterioration of immune system; hence, it is vital to interrogate immunity-related diseases with COVID-19 because COVID-19 was more prevalent in region with high IBD cases (Monteleone et al. 2020). The SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2) receptor expresses mainly in epithelial cells of lungs, colon, and ileum (Harmer et al. 2002). The expression of ACE2 was found to be increased in inflamed gut of IBD patients (Garg et al. 2020). About half of the COVID-19 patients' fecal samples were found positive for SARS-CoV-2 and one fifth of COVID-19 patients showed the presence of SARS-CoV-2 in stools after negative result in the respiratory sample (Xiao et al. 2020). This study showed that gut is potent source of viral reservoir. As discussed earlier, protease is produced by some pathogens found in pouchitis as well as they allow entry of host protease due to mucosa weakening. Above observations pointed out that IBD represent favorable environment for virus entry/persistence in human tissue (Jablaoui et al. 2020). Owing to this, COVID-19 patients need to follow five "F" factors (finger, flies, fluid, food, and fields) to prevent fecal transmission of SARS-CoV-2 (Dhar et al. 2020).

14.5 Probiotics in the Management of Pouchitis

The human gut microbiome, also referred to as the microbiota, consists of diverse bacteria, virus, archaea, and protozoa. The human microbiota is capable of modulating the immune system and avoiding predisposition to the disease. The gut microbiome is associated with multiple functions inside the human, including fermentation of starch, plant fiber into short-chain fatty acid (SCFA), source of vitamins, repression of pathogens, drug metabolism, maintenance of gut integrity, prevention of allergy, and also suppressing the onset of IBD (LeBlanc et al. 2021). Pouchitis is not totally attributed to a single microbe, but reduced microbiome diversity is common in pouchitis. Treatment with probiotics may improve pouch-related dysfunction irrespective of PDAI status (Fig. 14.2). Probiotics could be very

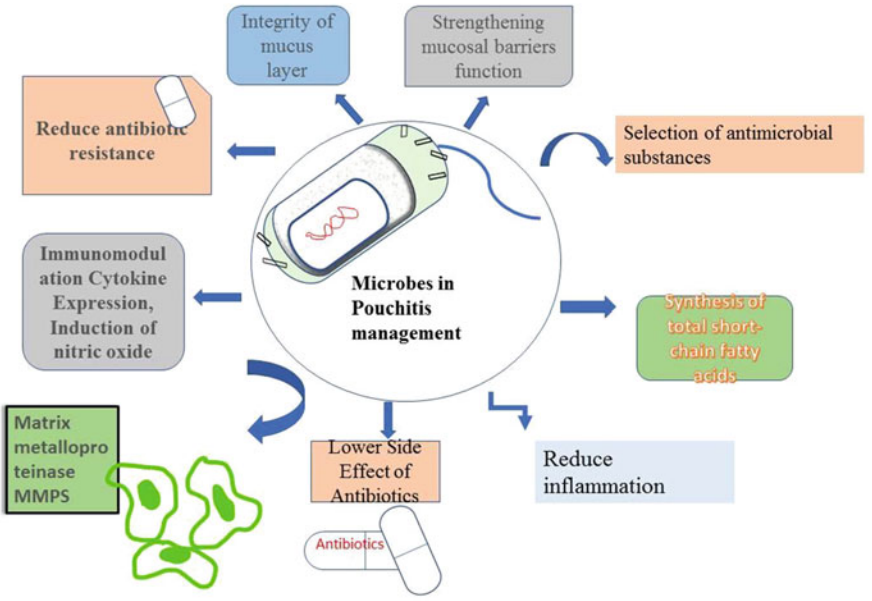

Fig. 14.2 Mode of action of useful microbes in pouchitis. Microorganisms by either direct involvement (synthesis of antimicrobial compounds, short chain fatty acids) or indirect involvement (delay in drug resistance, immunomodulation, mucus integrity) reduce pouch inflammation and relapse

useful in prophylaxis for pouchitis and preventing recurrence of pouchitis. The VSL#3 is a commercially available lyophilized probiotic consisting of four strains of *Lactobacillus* (*L. casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacterium* (*B. longum*, *L. breve*, and *B. infantis*), and one strain of *Streptococcus salivarius* subsp. *thermophiles*. Twenty-three active patients of pouchitis with PDAI scores between 7 and 12 were treated with a heavy dose of VSL#3 (2 sachets/day) for 4 weeks, followed by 1 sachet/day as maintenance treatment (Gionchetti et al. 2007). It was found that 16 of 23 patients (69%) were in remission after probiotic therapy. The author claimed that VSL#3 was able to treat active mild pouchitis with improved microbial, endoscopic, clinical, and histologic parameters on the PDAI, with complete remission in almost 70% of patients.

The immune system of the intestine is the largest part of the human immune system as it interacts with food antigens, commensal bacteria, and pathogens. Microbial metabolites play a key role in modulating the immune response. For example, lipopolysaccharide (LPS) from *E. coli* interacts with Toll-like receptors-4 (TLR-4), whereas lipopolysaccharide (LPS) from *P. gingivalis* interacts with TLR-2 receptors and both generate variable immune responses (Hirschfeld et al. 2001).

After VSL#3 administration, the fecal concentration of *Bifidobacteria*, *Lactobacilli*, and *S. thermophiles* increased significantly. The VSL#3 significantly enhanced tissue level of cytokine interleukin-10 (IL-10), an anti-inflammatory

cytokine, decreased the pro-inflammatory cytokines (IL-1, TNF-α, and IFN-γ), improved dendritic function, and reduced the metalloproteinase activity (Ulisse et al. 2001). Dendritic cells (DCs) play an important role in early pathogen recognition and appropriate T-cell response.

IL-10 controls mucosal inflammation by direct anti-inflammatory effect or by activating regulatory T cells. Metalloproteinase plays a vital role in the initiation of inflammation by degrading the basement membrane and extracellular matrix. The imbalance of metalloproteinase expression and activity during inflammation may have hazardous effects leading to loss of tissue integrity. Probiotic supports the nonspecific stimulation of host immunity and phagocytosis with enhanced production of IgA and may underlie their anti-inflammatory activity (Hart et al. 2004).

Inducible nitric oxide synthase (iNOS) increases macrophage action during inflammation, and its activity increased after cytokine stimulation. The iNOS activity in inflamed pouch was found to be 1.9 ± 0.6 pmol/mg protein/min while in control pouch it was reported to be 0.6 ± 0.2 pmol/mg protein/min. After the treatment with VSL#3, the iNOS activity decreased significantly (0.5 ± 0.2 pmol/mg protein/min) as compared to standard antibiotics (rifaximin and ciprofloxacin) (Ulisse et al. 2001). These findings suggest the beneficial role of probiotics in maintaining remission of chronic relapsing pouchitis.

Lactobacillus rhamnosus GG is highly effective against rotavirus and *C. difficile*. In a separate study, Kuisma et al. (2003) verified the potential of *L. rhamnosus* GG as therapy for pouch inflammation and its role in pouch microflora. *Lactobacillus* GG [$(0.5–1) \times 10^{10}$ colony-forming units/capsule] was administered twice daily for 3 months, and fecal samples and pouch biopsies were taken for microbial analysis. Interestingly, *Lactobacillus* GG increased the ratio of *Lactobacilli* to fecal anaerobes as well as the persistence of *Lactobacilli*-positive cultures in mucosal biopsy samples. However, colonization of *Lactobacillus* occurred in only 40% of pouchitis patients, and there was no significant difference in PDAI with and without *Lactobacilli* supplementation. The authors concluded the need for multiple useful microbes as a cocktail with variation in dosage in pouchitis treatment along with more robust clinical trials with a large number of patients and the factors important for adhesion and colonization of useful strains on the pouch mucosa.

Bengtsson et al. (2016) analyzed the potential of *Lactobacillus plantarum* 299 (5×10^9) and *Bifidobacterium infantis* cure 21 (5×10^9) to improve pouch dysfunction regardless of PDAI because these species have been used in the treatment of IBD. They analyzed biochemical markers of inflammation and histopathological study. The authors found that there is no improvement in pouch functional score (PFS) in pouch dysfunction after probiotic treatment. However, biomarker changes were significant such as calprotectin level decreased from 70.50 to 34.00 mg/kg, lactoferrin level from 1.65 to 0.70 μ/g, myeloperoxidase decreased to 2601 from 3997 ng/g and eosinophilic cationic protein from 35.50 to 15 μg/L. The authors discussed that use of only two strains of probiotics as compared with eight strains used in VLS#3 may be the crucial factor and emphasized correlating inflammation biomarkers with PFS and PDAI for pouchitis management. Few microorganisms' role in the management of pouchitis is summarized in Table 14.2.

Table 14.2 Microbes associated with the management of pouchitis

Sr. no.	Microbes in pouchitis management	Major findings for mechanism	References
1	*Ruminococcus gnavus*	Antibacterial compound synthesis	Dabard et al. (2001)
2	Enterococcaceae species	Maintaining immunologic homeostasis in the pouch mucosa	Kuehbacher et al. (2006)
3	*Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium bifidus*	43% remission rate; vs 0% on placebo	Tomasz et al. (2014)
4	*Bifidobacterium longum BB 536*	Pouchitis-free survival 86%, vs. 60% on placebo (NS); a small reduction in PDAI scores	Brown et al. (2004)
5	*Clostridium butyricum*	Pouchitis-free survival: 89%, vs. 50% on placebo (NS)	Yasueda et al. (2016)
6	*Lactobacilli and Bifidobacterium*	Symptomatic and endoscopic improvement in patients with active disease, symptomatic improvement	Laake et al. (1999)
7	*Lactobacillus rhamnosus GG*	Effective in the primary prophylaxis	
8	*Fusobacter and Enterobacters*	Proinflammatory cytokines leading to further increase in disease magnitude via inflammation-induced injuries.	Hessle et al. (2005)
9	*Bifidobacteria, Lactobacilli,* and *S. thermophiles*	Treat active mild pouchitis with improved microbial, endoscopic, clinical, and histologic parameters on the PDAI	Ulisse et al. (2001)

14.6 Fecal Microbiota Transplant in the Treatment of Pouchitis

Fecal microbiota transplant (FMT) was found to be an effective treatment in *C. difficile* infection, and its usefulness in irritable bowel syndrome (IBS) was also investigated (Halkjær et al. 2018). Very few reports are available regarding the use of FMT in acute pouchitis. The study conducted by Karjalainen et al. (2021) used fecal material from a healthy woman (52 years old) with normal body weight, no antibiotics or probiotics within the last 6 months, and did not have any intestinal symptoms. The same volunteer fecal sample was successfully used to treat recurrent *C. difficile* infection. Pouchitis patient (135) selection criteria include previous IPAA surgery for UC, endoscopically and histologically diagnosed pouchitis within 6 months before FMT, and antibiotics therapy because of the chronic pouchitis. After completion of the study protocol, it was concluded that FMT was well tolerated and did not cause any adverse effects, but FMT was not effective in the treatment of chronic pouchitis. Five patients in the FMT group relapsed before the second fecal transplant, whereas in the placebo group, no one relapsed during the

first 4 weeks. However, the present study needs more elaborated experimentation with multiple factors under consideration, such as pre-selection of the fecal donor based on microbiota characteristics, interference of antibiotics, microbial load in FMT sample. Further studies needed to be done regarding evaluating the usefulness of FMT in pouchitis as FMT has some advantages, such as cost-effectiveness, than biologic therapy and can prevent the risk of antibiotic resistance.

14.7 Conclusions

In summary, dysbiosis plays a significant role in pouchitis, where pathogenic microbes dominate the pouch with proinflammatory and homeostatic disturbances. Extensive use of antibiotics in pouchitis treatment results in nonspecific eradication of useful and native pouch microbial population, giving an opportunity for opportunistic pathogens to colonize and generate inflammation in the pouch. But the addition of useful microflora improves the barrier function of mucosa and normal pouch functions. Therefore understanding the role of pathogenic microbes in the inflamed pouch will be very useful for safe and effective treatment. At the same time use of manipulation of microbiota via probiotics, fecal microbial transplantation is promising therapeutic candidates in pouchitis treatment. However, microbes differ from one to another at strain level, and hence, there is need of robust study of formulation doses consisting of multiple strains with pouch disease activity index, colonization, impact on immunomodulation, and inhibition of pathogens responsible for pouch inflammation. At present, the availability of less data, small sample size, variation in diagnostic criteria hinder the progress of microbial management of pouchitis. Microbes can be used as a synergistic agent along with traditional and emerging therapies (antibiotics, biological, and prebiotics) to enhance the clinical benefits of pouchitis.

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Microorganisms in the Pathogenesis and Management of Celiac Disease (CeD)

15

Arshdeep Singh, Harmeet Kaur, Vandana Midha, and Ajit Sood

Abstract

Celiac disease (CeD) is an autoimmune enteropathy caused by an aberrant immune response to gluten in genetically susceptible individuals. Though the data are heterogeneous, there is growing evidence to support that alterations in the composition and functions of the intestinal microbiota as well as infectious exposures in early childhood are associated with CeD. However, the mechanisms by which microorganisms contribute to the development of CeD remain elusive and the causal association between microorganisms and CeD has not been established. This chapter summarizes the available evidence on the interrelation between microorganisms and CeD describing the role of microorganisms in specific pathways involved in the pathogenesis of disease. Understanding the role of microorganisms in the pathogenesis of CeD would help to develop and refine microbiota modulating tools such as probiotics, prebiotics, microbe-derived gluten degrading enzymes, and fecal microbiome transfer, that can be used as therapeutic agents in CeD.

Keywords

Celiac disease (CeD) · Gastrointestinal microbiome · Gluten · Microbiota · Probiotics · Prebiotics

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15.1 Introduction

Celiac disease (CeD) is a systemic, chronic, inflammatory, autoimmune enteropathy that affects approximately 1% of the global population (Singh et al. 2018). The disease is characterized by T-cell-mediated damage to small bowel mucosa caused by ingestion of gluten in genetically susceptible individuals. Though both genetic susceptibility and exposure to gluten are required, these alone are not sufficient, and an additional predisposing factor is necessary for the development of CeD. This is supported by the fact that nearly one third population of the world carries the celiac compatible HLA haplotypes (HLA DQ2 and/or HLA DQ8 genes), and yet only 1% of the population develops CeD (Yuan et al. 2013; Rostami-Nejad et al. 2014; Singh et al. 2018; Caio et al. 2019). Additional non-HLA genes have been identified in patients with CeD, though their clinical relevance is unclear. The other predisposing factors for CeD apart from genes and dietary gluten are the environmental influences, of which the intestinal microbiota has emerged as an important determinant. Given the myriad functions performed by the intestinal microbiota in maintaining gut homeostasis, facilitating digestion and absorption, and modulating the immune responses of the host by maintaining a balance between immune-competence and immune-tolerance, it is not surprising that alteration in the composition and function of microbiota is associated with the development of the disease (Feng et al. 2018). Implicated in disease pathogenesis, microbiota presents itself as an attractive target for use as a therapeutic agent. This chapter reviews the pathogenesis and management of CeD in light of the role played by intestinal microbiota.

15.2 Pathogenesis of Celiac Disease

Gluten, a protein composed of a complex group of alcohol-soluble gliadins and alcohol-insoluble glutenins, is the primary environmental trigger for CeD. Both the time of introduction of gluten in diet and the amount of gluten ingested have been implicated in the pathogenesis of CeD. Gliadins are digested partially by the proteolytic enzymes present in the intestinal lumen. These partially digested gliadin peptides (GP), via paracellular (through zonulin, that disintegrates intercellular tight junctions) and transcellular pathways, gain entry to the lamina propria, where, after deamidation by tissue transglutaminase (tTG2), they initiate aberrant innate [characterized by high interleukin 15 (IL15), interleukin 8 (IL8), and intraepithelial lymphocytes]; and adaptive and humoral (characterized by Th1- and Th17-mediated increased production and release of pro-inflammatory cytokines, and activation of B cells) immune responses. The pro-inflammatory milieu in the lamina propria damages the enterocytes, that further compromises and disrupts the intestinal barrier, and in the process compounds the immune-mediated injury to the enterocytes (Kupfer and Jabri 2012; Tye-Din et al. 2018).

CeD has a strong genetic component with high prevalence in monozygotic twins and first-generation relatives. The HLA genes play an important role in recognizing and presenting the deamidated GPs to T cells, activating the downstream cascade of

production of inflammatory cytokines. The non-HLA genes have also been hypothesized to regulate intestinal permeability, proliferation of B and T cells and pro-inflammatory cascade (Sharma et al. 2016). Figure 15.1 shows a schematic representation of the pathogenesis of CeD.

Intestinal microbiota plays an important role in the pathogenesis of CeD as it interacts with both gluten (the environmental trigger) and the genes (the susceptive host). Furthermore, the intestinal microbiota maintain the integrity of the intestinal epithelium, and the products of microbial metabolism modulate the inflammatory immune response. Though the intestinal microbiota comprises of bacteria, fungi, viruses, archaea, protozoa, and helminths; the bacteria are the most abundant and widely studied group of microorganisms. In the current chapter therefore, the term microbiota would primarily refer to intestinal bacteria. A detailed discussion on the role of fungi, viruses, and other microorganisms is beyond the scope of the chapter and has been discussed elsewhere in literature.

15.3 Dysbiosis in CeD

Using the gnotobiotic approach, the germ-free rats fed with gliadin were found to develop more severe intestinal damage as compared to the rats with normal intestinal microbiota (Stěpánková et al. 1996; Galipeau et al. 2011), suggesting that the intrinsic anti-inflammatory properties of the normal intestinal microbiota have the capacity to reduce the pro-inflammatory effects of gluten. Microbial dysbiosis (defined as a change in the structure and/or function of the resident intestinal microbiota) is therefore expected to predispose to the development and progression of immune-mediated damage in CeD. Duodenal mucosal biopsies as well as fecal samples from patients with CeD have demonstrated an altered microbial profile, though no specific group of microbes has been established as the cause.

Patients with active disease have shown increased abundance of *Clostridia* spp., *Bacteroides* spp., and *Prevotella* spp. and decreased abundance of *Lactobacillus* spp., *Enterococcus* spp., and *Bifidobacterium* spp. in the duodenal biopsy and fecal samples (Collado et al. 2009; De Palma et al. 2010b; Di Cagno et al. 2011). Further, Di Biase et al. reported *Enterobacteria* to be more abundant in the duodenal biopsies of untreated CeD patients as compared to *Bacteroidetes* or *Streptococcus*, whereas *Bacteroides-Prevotella*, *Akkermansia*, and *Staphylococcaceae* had lower abundances in the fecal samples of the same patients (Di Biase et al. 2021). Recently, a specific fecal microbiota signature for CeD, with decreased abundance of 11 operational taxonomic units (OTUs), the two most common being OTU_531 *Clostridium* sensu stricto and OTU_143 *Ruminococcus*, has been described in Scottish children, though it needs validation across larger and ethnically distinct populations (Zafeiropoulou et al. 2020). A low ratio of lactic acid bacteria-*Bifidobacterium* vs *Bacteroides-Enterobacteria* in feces or duodenal biopsy, as compared to healthy controls, characterizes CeD (Macfarlane et al. 1998; Di Cagno et al. 2009, 2011). High *Escherichia coli* and *Staphylococcus* and low *Lactobacillus* prevalence have been observed in individuals with CeD when compared to healthy controls (Schippa

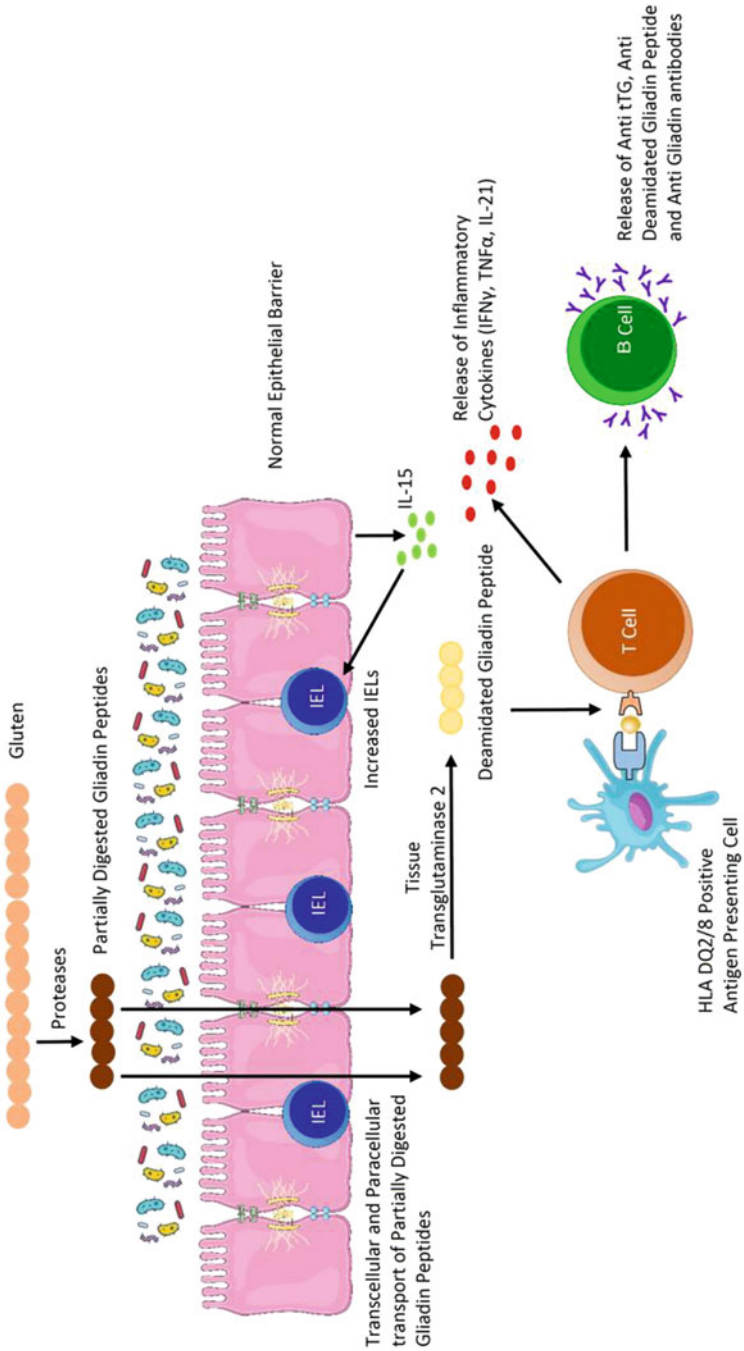

Fig. 15.1 Schematic representation of pathogenesis of celiac disease

Table 15.1 Intestinal bacterial dysbiosis in celiac disease

Increased abundance	Decreased abundance
Bacteroides spp.	*Lactobacillus* spp.
Escherichia coli	*Bifidobacterium* spp.
Staphylococcus spp.	*Akkermansia muciniphila*
Neisseria spp.	*Faecalibacterium*
Gram-negative bacteria	*Clostridium* cluster XIVa

et al. 2010; Sánchez et al. 2013; Lorenzo Pisarello et al. 2015). Pro-inflammatory microbial dysbiosis is also associated with symptoms of CeD. Overrepresentation of *Proteobacteria* has been reported to correlate with disease activity. Increased frequency of *Bacillaceae* and *Enterobaeriaceae* correlated with abdominal pain, whereas an increase in *Bacillaceae* and *Fusobacterium* and reduction in *Clostridium* cluster XIVa and *Akkermansia* correlated with diarrhea (Di Biase et al. 2021).

To summarize, the published studies on characterization of microbiota in CeD demonstrate an increased abundance of Bacteroides (*Bacteroides vulgatus* and *Bacteroides fragilis*), *Escherichia coli* and *Staphylococcus* spp. and decreased *Lactobacillus* spp., *Bifidobacterium* (*Bifidobacterium longum*), and *Akkermansia muciniphila* in the duodenal biopsy or fecal samples. The studies on prevalence of *Prevotella* in patients with CeD are conflicting and inconsistent. The bacterial dysbiosis observed in CeD is summarized in Table 15.1.

15.4 Role of Intestinal Microbiota in the Pathogenesis of CeD

Whether the association between bacterial dysbiosis in CeD is causal or not is a matter of debate. However, the intestinal microbiota dysbiosis remains at the center of disease pathogenesis (Fig. 15.2). The interplay between microbiota and specific pathways involved in the development of disease are discussed in the following sections.

15.4.1 Interactions Between HLA DQ Haplotypes and Microbiome

Associations between intestinal microbiota, host genetics, and single-nucleotide polymorphisms (SNPs), studied by two-sample Mendelian randomization analysis, have revealed that all the CeD SNPs identified themselves with *Firmicutes* and *Proteobacteria* phyla, thereby suggesting that the intestinal microbial composition in at-risk infants is influenced by the genetic make-up (García-Santisteban et al. 2020).

At phyla level, an increased abundance of *Firmicutes* and *Proteobacteria* and decreased abundance of *Bacteroidetes* and *Actinobacteria* have been seen in the fecal samples before the onset of disease in infants carrying celiac compatible HLA haplotypes (Sellitto et al. 2012). A higher *Bacteroides-Prevotella* proportion and an increased abundance of Gram-negative bacteria, *Streptococcus*, *Lactococcus*, and *Clostridium histolyticum* have been reported in high-risk infants in another study

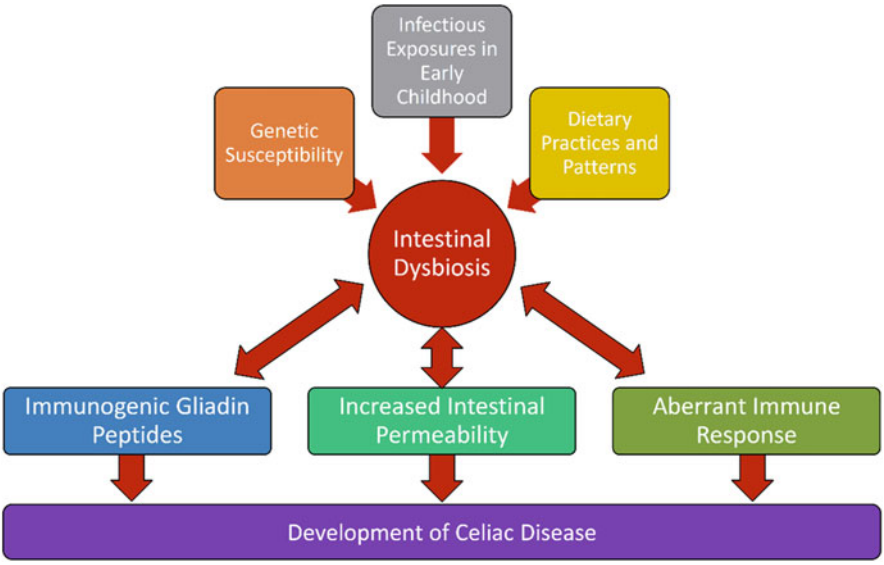

Fig. 15.2 Flow diagram depicting intestinal dysbiosis at the center of pathogenesis of celiac disease

(De Palma et al. 2010a). Other bacterial genera that are altered in at-risk patients include *Streptococcus*, *Coprococcus*, *Veillonella*, *Parabacteroides*, and *Clostridium perfringens* (Leonard et al. 2020).

Lower prevalence of *Bifidobacterium longum* has been reported in at-risk infants and infants with family history of CeD (Olivares et al. 2015, 2018). This suggests that genetic susceptibility to CeD inhibits the colonization of protective, anti-inflammatory bacteria such as *Bifidobacterium* in the gut, enhancing the risk for development of disease.

The presence of HLA haplotypes also influences the dynamics of intestinal microbiota. Various microbial metabolism and functional pathways have been reported deficient in infants between the ages of 4 and 6 months. The metabolites that are altered in genetically predisposed infants are butanoic acid (increased) and dihydroxyacetone (decreased) (Leonard et al. 2020).

The phylogenic diversity of the intestinal microbiota increases with age during infancy. However, it has been observed that in patients at risk for CeD, the phylogenic diversity does not increase significantly over time. This uncommon pattern of premature maturation of the intestinal microbiota during early stages of life is another way by which the genes influence the microbiome predisposing to CeD (Olivares et al. 2018). On the contrary, a delayed stabilization of the intestinal microbiota occurring beyond 12–24 months of age in genetically at-risk infants has also been described (Sellitto et al. 2012). The host genetics, apart from the environmental (e.g., feeding practices) influences, plays a major role in these abnormalities

in the time-related development, maturation, and stabilization of the intestinal microbiota.

These observations lead to the hypothesis that specific host genotype determines the composition of intestinal microbiota. The genetic make-up of the host selects specific microbial colonizers and rejects others to vest an increased risk of CeD.

15.4.2 Interactions Between Gluten and Microbiome

Pseudomonas aeruginosa (belonging to phyla *Proteobacteria*) has proteolytic activity against the immunogenic GPs (produced by partial digestion of gluten). Proteolysis of these GPs produces smaller peptides that rapidly cross the intestinal mucosal barrier and elicit a heightened immune response from gluten-specific T cells. On the contrary, *Lactobacillus* degrades and converts the immunogenic peptides (33-mer peptide) to non-immunogenic peptides (Caminero et al. 2016). *Lactobacillus* has also shown the ability to reduce intestinal inflammation by degrading the wheat amylase trypsin inhibitor in HLA $DQ8^{+}$ mice (Caminero et al. 2019a, b). *Bifidobacterium* strains also attenuate intestinal inflammation by modifying the toxic GPs generated during digestion (Laparra and Sanz 2010). Other oral (*Rothia*, *Streptococcus*, *Neisseria* and *Capnocytophaga*) and intestinal (*Bacteroides*, *Lactobacillus*, *Streptococcus*, *Staphylococcus*, and *Clostridium*) bacteria-derived enzyme activities also play an important role in the digestion of gluten (Herrán et al. 2017). Thus, intestinal bacteria have different activities and different metabolic patterns to handle digestion of gluten.

15.4.3 Interactions Between Microbiome and Intestinal Barrier

Maintaining intestinal barrier is an important step in preventing gluten sensitivity as increased mucosal permeability (both paracellular and transcellular) allows enhanced passage of immunogenic GPs into the lamina propria where they initiate the cascade of an aberrant immune response. The leaky intestinal barrier in CeD can be due to either activation of molecular pattern recognition receptors or modifications in the mucus layer or tight junctions.

The expressions of molecular pattern recognition receptors, Toll-like receptors (TLR), especially TLR2 and TLR9, and Toll-interacting protein (TOLLIP), are altered in duodenal biopsies of patients with CeD, suggesting the role of microbiota-associated factors in the pathogenesis of CeD (Kalliomäki et al. 2012). Also, pathogenic bacteria, via activation of TLR-4 and CD14, activate the innate immune system to produce pro-inflammatory cytokines. CXCL10 is a ligand for CXCR3 and the CXCL10/CXCR3 complex activates zonulin to increase the intestinal permeability. The CXCL10/CXCR3 axis can also be activated by bacterial antigens amplifying the gluten-induced inflammatory process (Heyman et al. 2012).

Animal studies have demonstrated the deleterious effects of *Enterobacteria* (*Escherichia coli* and *Shigella*) on the goblet cell numbers and integrity of tight

cell junctions in CeD (Cinova et al. 2011). *Bacteroides fragilis* and *Escherichia coli* also express metalloproteases that increase the intestinal permeability by the disruption of tight junctions (Glotfelty et al. 2014; Ménard et al. 2012). In contrast, *Bifidobacterium bifidum* and *Lactobacillus rhamnosus* are known to increase the number of goblet cells, produce metalloproteinase inhibitors, decrease the expression of NF-κB and chemokine CXCR3 receptors, contributing to maintenance of intestinal barrier and reduced translocation of GPs to lamina propria (Cinova et al. 2011; Orlando et al. 2014). Furthermore, *Akkermansia muciniphila*, a symbiont bacteria that regulates the synthesis of mucin, is deficient in CeD. The deficiency of *Akkermansia* impairs the mucin production to compromise the intestinal barrier (Bodkhe et al. 2019).

Short-chain fatty acids (butyrate in particular), produced by intestinal bacteria, have also been shown to regulate intestinal permeability and epithelial integrity by upregulating the gene expression of barrier proteins in CeD-derived organoids (Freire et al. 2019). *Lactobacillus rhamnosus* GG has been demonstrated to protect the epithelial barrier in Wistar rats from GP-induced enteropathy by favorably impacting the intestinal mucosal architecture and upregulating the expression of intercellular junction proteins (zonulin, occludin, claudin-1, β-catenin, and E-cadherin). However, the beneficial effects are observed only in animal models and that too once the enteropathy has set in. No protective or prophylactic effects of *Lactobacillus rhamnosus* have been elicited in human studies, as yet (Orlando et al. 2018).

The intestinal epithelial cells also maintain the sterility of the mucous layer by producing antibacterial C-type lectin (RegIIIγ). The production of RegIIIγ is regulated by the intestinal microbiota. The deficiency of RegIIIγ results in microbiota-dependent increase in Th1 cells in the lamina propria disrupting the immune homeostasis (Krishnareddy 2019). The microbes are therefore vital to maintain the functionality of the intestinal barrier. Disruption of the intestinal epithelium by dysbiotic microbes grants access to the GPs and other immunogenic bacterial peptides to gain entry to the lamina propria, favoring the development of CeD.

15.4.4 Interactions Between Microbiome and Immune Response in Celiac Disease

Microorganisms are vital for the maintenance of the architecture of the gastrointestinal immune system. Apart from maintaining the mucosal barrier between microbe-rich intestinal lumen and epithelial cells, the microbiota stimulate the formation of gut-associated lymphoid tissue (GALT) and regulate the immune responses by modulating the synthesis and function of various immune mediators.

The GALT synthesizes IgA in response to the identification of the non-commensal bacterial antigens in the intestinal lumen. The secreted IgA coats these bacterial antigens and limits the immune responses to the mucosal surface only, avoiding systemic inflammation. The secretion of IgA is dependent on the

microbiota. Germ-free (GF) mice have been shown to have reduced germinal centers in GALT, impairing the immunomodulatory properties intrinsic to GALT. *Bifidobacterium* species have been demonstrated to stimulate the synthesis of secretory IgA in Swedish infants, protecting against autoimmunity (Sjögren et al. 2009).

CeD is associated with increased intra-epithelial lymphocytes (IELs). The intestinal microbiota can affect the distribution and function of IELs through TLRs, NOD-2, or the aryl hydrocarbon receptors. *Pseudomonas aeruginosa* expresses gluten degrading proteases, which, through PAR-2 signaling, induce an innate immune response increasing the number of IELs. Animal studies have shown this induction of IELs by *Pseudomonas aeruginosa* to be independent of gluten, though the effect is synergistic (Caminero et al. 2019a).

The Paneth cells in the intestinal epithelium secrete defensins (the natural antimicrobials of the intestinal tract) and regulate the intestinal microbiota composition. The secretion of defensins is controlled by specific bacteria present in intestinal crypts. In patients with active CeD, the number of Paneth cells and levels of B-defensins are decreased. Treatment of CeD with gluten-free diet (GFD) restores the microbial dysbiosis as well as the normal levels of B-defensins, suggesting normalization of Paneth cell function (Tobi et al. 2021). There is currently a wide knowledge gap between Paneth cells, microbiome, and CeD, which needs to be bridged by performing focused research in future.

The immune responses in CeD are characterized by an upregulated Th1 cell-mediated immune response effected via macrophages, cytotoxic $CD8^+$ T cells, IFNγ and $CD4^+$ T cells. Studies have shown that increased expression of Th1 cytokines in CeD is partly contributed by microbial dysbiosis. The intestinal microbiota maintain the Th1/Th2 balance. *Bifidobacterium* and *Lactobacillus* species suppress the Th1-dependent pro-inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1β, and IFNγ) abating the pro-inflammatory milieu and reinstating the Th1/Th2 balance (Medina et al. 2007, 2008; Baba et al. 2008; D'Arienzo et al. 2011; Palma et al. 2012). Reduced predominance of *Bifidobacterium* and *Lactobacillus* in CeD therefore augments the aberrant immune responses in CeD. Furthermore, the mucosal IL17A immune response is not seen uniformly in all the patients. The inconsistency of IL17A-driven immune response can be explained by the isolation of *Lachnoanaerobaculum* spp. and *Actinomyces* spp. in some patients of CeD. These bacteria trigger the IL17A-mediated immune response (Sjöberg et al. 2013).

Commensal *Clostridia* (Cluster IV and IVa) are inducers of regulatory T cells (Tregs). Reduced prevalence of these clusters in CeD affects the induction of Tregs, throwing the intestinal homeostasis into disarray (Cheng et al. 2013). Bacterial dysbiosis (predominance of *Escherichia*, *Neisseria*, and *Staphylococcus*) in CeD is also associated with increased expression of virulent genes and pro-inflammatory cytokines in vitro (Sánchez et al. 2012). The products of bacterial metabolism, specifically the SCFAs, also modulate the immune responses. Altered production of butyrate and lactate in CeD triggers posttranslational modifications (epigenetic switch between the two isoforms of the forkhead box protein 3) impairing the immune-suppressive functions of Tregs (Serena et al. 2017).

Furthermore, some intestinal bacteria express epitopes that mimic gliadin, and the molecular mimicry may potentially trigger immune responses. Two major peptides from *Pseudomonas fluorescens* have been demonstrated to cross react with immune stimulatory gliadin epitopes. This cross-reactivity is proposed to be based on functional molecular mimicry between peptide sequences from specific bacteria and T-cell immunogenic gluten peptides (Petersen et al. 2020). However, the translocation of the bacterial peptide sequences into the lamina propria, which houses the adaptive immune system, and the enterocyte damage induced by these peptides need to be evaluated in detail. The immune responses in CeD are thus shaped by, in addition to the immunogenic effects of gluten, the intestinal microbiota. Fig. 15.3 depicts the different steps at which microbiota interact with the host during the development of CeD.

15.5 Role of Infections in the Development of CeD

Infections during early childhood, especially during neonatal period, have been associated with the subsequent development of CeD. Repeated or persistent infections result in constant low-grade intestinal inflammation (through molecular mimicry, intestinal dysbiosis, or infection/inflammation-driven activation of immune responses) that breaks down gluten tolerance in genetically predisposed individuals. The common offenders are *Campylobacter jejunii*, *Clostridium difficile*, *Streptococcus pneumoniae*, *Rotavirus*, *Adenovirus*, *Reovirus*, and *Enterovirus* (Sánchez et al. 2021; Størdal et al. 2021). Interestingly, infections with cytomegalovirus (CMV), Epstein–Barr virus (EBV), and *Helicobacter pylori* have been reported to be protective against CeD (Lerner et al. 2017). The protective effects are hypothesized to be mediated through the alteration of host immune response, reduction of gluten immunogenicity, and modulation of intestinal permeability (Lerner et al. 2017). However, the long lag time between exposure to infectious agents and development of disease makes it difficult to establish the exact relationship between the two. Repeated longitudinal sampling is required to determine the differences between colonization and clinical disease. If the causal relationship is established, vaccination against the offending infectious agents could prevent the development of CeD.

15.6 Microbiota Targeted Therapy for CeD

The cross talk of intestinal microbiota with host genetics, gluten, intestinal epithelial barrier, and the immune system makes microbiota an attractive therapeutic target for the treatment of CeD. The modulation of intestinal microbiota can be done by diet (GFD for CeD), antibiotics, pre/probiotics, and fecal microbiome transfer (FMT). Each of these approaches has been explored as therapy for CeD, with variable success. Additionally, microbiota-derived enzyme-based therapy and specific microorganism-based therapy have also been tested (Table 15.2).

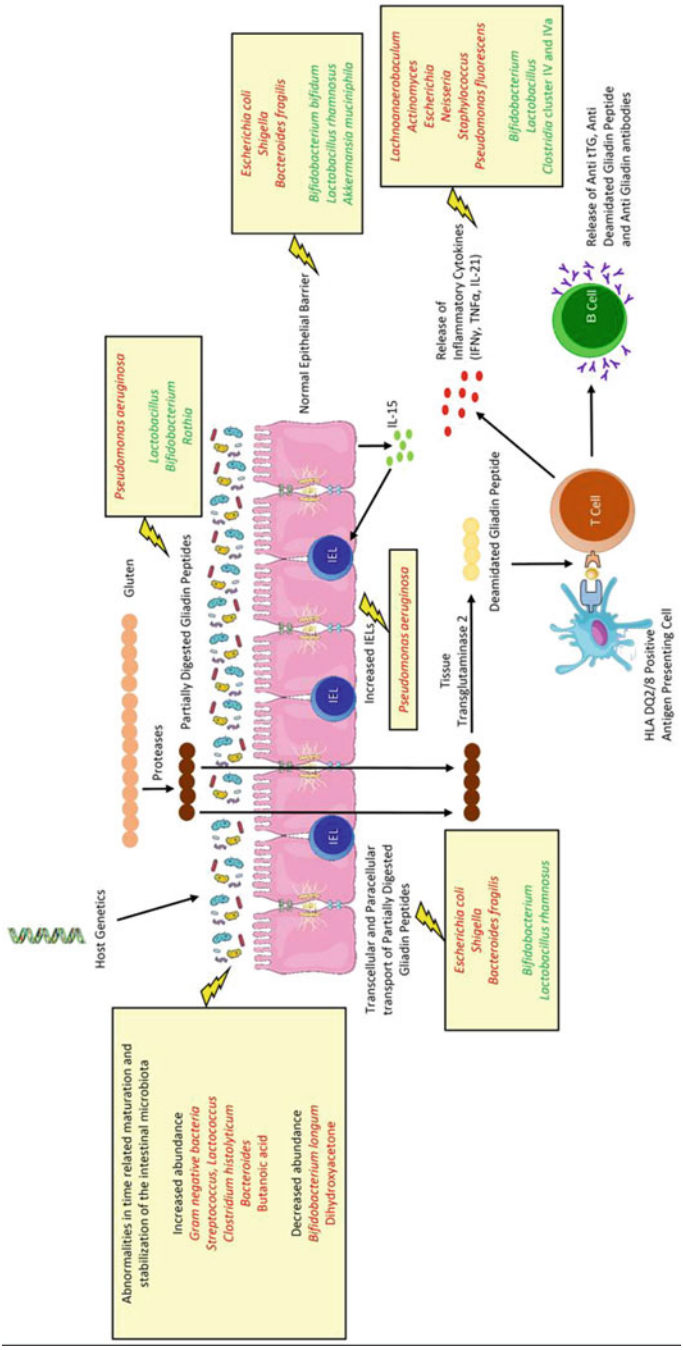

Fig. 15.3 Interactions of intestinal microbiota with specific pathways in the development of celiac disease (CeD). The microbes involved at a particular step in the pathogenesis of celiac disease are depicted in yellow boxes. Microbes written in red increase the susceptibility to develop celiac

15.6.1 Dietary Intervention: GFD

The composition of intestinal microbiota is determined by the dietary patterns and practices. The only accepted treatment of CeD to date is GFD. GFD reduces the clinical symptoms and reverses the enterocyte damage induced by gluten and microbial immunogenic peptides. However, the effect of GFD on the composition of the intestinal microbiota is inconsistent across different studies. Though the intestinal bacterial diversity has been demonstrated to improve on GFD, it is not completely restored. Between treated and untreated patients of CeD, differences in abundances of 39 OTUs have been observed (Zafeiropoulou et al. 2020). *Bifidobacterium* and *Lactobacillus* prevalence has been reported to be lower on GFD as compared to healthy controls, though the relative abundance was greater as compared to untreated CeD (Collado et al. 2008; Di Cagno et al. 2009; Golfetto et al. 2014).

In children treated with GFD, high frequencies of *Bacteroides*, *Staphylococcus*, *Salmonella*, *Shigella*, and *Klebsiella* have also been documented in fecal samples, when analyzed by culture-dependent methods (Di Cagno et al. 2011). Mucosal healing occurring on GFD also determines the microbial composition. The differences in the composition of intestinal microbiota on GFD can be explained to some extent by changes in the dietary patterns after initiation of GFD (reduced intake of complex carbohydrates and fiber) and may not only be a result of the disease effect. Similar changes in the intestinal microbiota, in patients on GFD who received dietary interventions for diseases other than CeD, corroborate this hypothesis. The differences in the microbial signals on GFD, as compared to untreated disease, indicate toward modulation of microbiota with GFD, and identification of these bacteria could guide the development of immune modulating microbial therapeutics.

15.6.2 Probiotics

Probiotics are live microorganisms, which when ingested in adequate amounts, confer health benefit to the host. Acknowledging the direct as well as indirect role of microorganisms in the pathogenesis, probiotics have been tested as therapy in multiple in vitro and in vivo studies to assess the benefits of probiotics in regulating and harmonizing the microbial dysbiosis associated with CeD. Additionally certain probiotics are also known to have intrinsic anti-inflammatory properties that may lessen the gluten-derived inflammation, suggesting therapeutic benefits. The effects of probiotics on clinical symptoms, quality of life (QoL), levels of inflammatory cytokines, and intestinal permeability have been evaluated and reported in literature.

Fig. 15.3 (continued) disease, while those written in green have protective effect and have the potential to be used as therapy for celiac disease

Table 15.2 Microbiota targeted therapies for celiac disease

Therapy	Effect on					References
	Clinical symptoms	Quality of life	Inflammatory cytokines	Intestinal permeability	Mucosal healing	
Gluten-free diet	Improve	Improve	Decrease	Decrease	Occurs	
Probiotics	Improve	No effect	Decrease, the levels increase on stopping probiotics	Conflicting data	Not known	Seiler et al. (2020)
Prebiotics	Not known	Not known	Not known	Not known	Not known	Capriles and Arêas (2013), Krupa-Kozak et al. (2017)
Fecal microbiome transfer	Not known	Not known	Not known	Not known	Not known	ClinicalTrials.gov identifier NCT04014413
Microbiota-derived glutenases	Not known	Not known	Decrease	Not known	Not known	Lindfors et al. (2008), Mandile et al. (2017), Francavilla et al. (2019), Caminero et al. (2019a, b)
Helminth therapy	Not known	Not known	Not known	Not known	Not known	Croese et al. (2015)

Lactobacillus strains and *Bifidobacterium* spp., either alone or in combination, are the most widely studied probiotic bacteria in CeD.

Use of probiotics in CeD is associated with improvement in gastrointestinal symptoms (abdominal distension, bloating, diarrhea, constipation, abdominal pain, and vomiting) as compared to placebo (Smecuol et al. 2013; Olivares et al. 2014; Francavilla et al. 2019). A systematic review and meta-analysis found that ingestion of probiotics was associated with an improvement in GI symptoms in patients with CeD. However, the quality of evidence for overall improvement in gastrointestinal symptoms is low and has a high risk of being biased (Seiler et al. 2020). Only two studies have reported the effects of probiotics on QoL, and a pooled analysis did not demonstrate improvement in QoL of CeD patients with probiotics (Harnett et al. 2016; Francavilla et al. 2019).

The effect of probiotics on serum concentration of inflammatory cytokines has been reported. A mixture of GPs and *Bifidobacteria* has been reported to down regulate the synthesis and release of pro-inflammatory cytokines in vitro (Medina et al. 2008; Laparra and Sanz 2010). Probiotic *Saccharomyces boulardii* KK1 strain, in mice studies, has been associated with a decreased production of inflammatory cytokines and reversal of histological changes (Papista et al. 2012). In adults with CeD, *Bifidobacteria*-based probiotics decrease the concentration of serum TNF-α (Primec et al. 2019). In children, however, the values decrease initially, but the effect was seen to wane 3 months after stopping probiotics, suggesting continuous rather than intermittent administration of probiotics is beneficial (Klemenak et al. 2015).

In vitro studies have shown decreased intestinal permeability with the use of *Lactobacilli* and *Bifidobacterium* strains in a dose-dependent manner (Lindfors et al. 2008). However, in an RCT, the intestinal permeability, as measured using lactulose/mannitol ratio, did not decrease with the use of probiotics when compared to placebo (Smecuol et al. 2013). The probiotics (*Saccharomyces boulardii*, *Bifidobacteria*, and *Lactobacilli* strains) have also been demonstrated to alter the host immune response by blocking toxin receptors, secreting SCFA and other antimicrobial peptides, regulating intraluminal pH and promoting B-cell maturation in in vitro and animal studies (Chibbar and Dieleman 2019). However, studies evaluating these effects in humans are lacking at present.

Most of the human intervention studies on the role of probiotics in CeD have been carried out in patients on GFD, which itself is known to modulate the intestinal microbiota and restore integrity of the intestinal epithelial barrier. The effects of probiotics on the various pathophysiological mechanisms, independent of the GFD are unknown and need to be evaluated. The gluten content in commercially available probiotics is another concern (Nazareth et al. 2015).

15.6.3 Prebiotics

Prebiotics are substances that promote the growth of microorganisms that contribute to the health of the host. The dietary prebiotics are usually non-digestible fibers. However, various functional foods (such as fermented foods with live cultures,

garlic, and curcumin) also have prebiotic properties. Studies are ongoing to determine the daily serving dose of prebiotics. Also addition of prebiotics (inulin-type fructans) to GFD has been proposed to improve calcium absorption in patients with CeD (Capriles and Arêas 2013). In another study, addition of oligofructose-enriched inulin to GFD increased the total SCFAs in patients with CeD by providing a ready source of energy to the intestinal microbiota (Krupa-Kozak et al. 2017).

15.6.4 Microbiota-Derived Glutenases

Several bacterial enzymes such as prolyl endopeptidases (PEPs), cysteine proteases, and subtilisins can cleave gluten and GPs. The bacterial PEPs are derived from *Flavobacterium meningosepticum*, *Sphingomonas capsulate*, *Myxococcus xanthus*, and *Aspergillus niger*. The proenzyme for glutamine-specific cysteine protease has been isolated from *Escherichia coli*. Subtilisins are derived from *Rothia mucilaginosa* (Shan et al. 2004; Bethune et al. 2006; Zamakhchari et al. 2011; Wei et al. 2020).

Bifidobacteria, via proteolytic enzymes, have been demonstrated to degrade the proinflammatory GPs, reducing their immunogenicity (Lindfors et al. 2008). *Lactobacilli* also secrete degrading enzymes that digest other non-gluten wheat proteins and amylase-trypsin inhibitors (ATIs) resulting in decreased inflammatory stress and improved intestinal permeability (Caminero et al. 2019b). The oral commensal bacteria (*Rothia*, *Actinomyces*, *Neisseria*, *Capnocytophaga*, etc.) also synthesize and secrete enzymes that hydrolyze and degrade the toxic gluten epitopes rendering the GPs less or non-immunogenic (Fernandez-Feo et al. 2013). In an in vitro study, there was no increase in the levels of inflammatory cytokines in duodenal biopsies obtained from CeD patients who consumed hydrolyzed wheat bread produced with *Lactobacilli* strains (Rizzello et al. 2007). In vivo studies have also reported encouraging results with consumption of *Lactobacilli* pre-digested wheat bread (Mandile et al. 2017; Francavilla et al. 2019). These observations suggest the role of *Lactobacilli*-derived endopeptidases in mitigating the gluten toxicity for CeD patients.

However, until the specific immunogenic GPs are not cleaved and degraded rigorously, the peptides can cross the epithelial barrier and elicit an aberrant immune response. Therefore, identifying the precise and discrete gluten degrading enzymes (glutenases) and testing them systematically in large randomized studies holds the key for use of microbe-derived glutenases on a large scale.

15.6.5 Hookworms

In a pilot study, hookworm (*Necator americanus*) larvae were inoculated in adult CeD patients on GFD. Gluten challenge (gluten consumed as pasta) was given in escalating doses after hookworm inoculation. Experimental infection with hookworms did not result in elevation of anti-tTG titres or villous atrophy on

histology, implying improved gluten tolerance (Croese et al. 2015). Further evaluation is needed before classifying helminths as therapy for CeD.

15.6.6 Fecal Microbiome Transfer (FMT)

FMT has emerged as a novel tool to modulate the intestinal microbiota and has been used successfully for the treatment of *Clostridium difficile* infection and inflammatory bowel disease (IBD). At present only one clinical trial (NCT04014413) evaluating the role of FMT in CeD is underway.

15.7 Conclusion

CeD provides a unique model to study the impact of microorganisms in a noninfective chronic genetically mediated inflammatory disease. The strong influence of microorganisms on each step in the pathogenesis of CeD, starting from genetic predisposition to gluten digestion to elicitation of an aberrant immune response, has been demonstrated beyond doubt. Additionally, specific changes in the composition of intestinal microbiota have been reported in case–control and cross sectional studies. Microbiota targeted therapies such as probiotics have also been investigated with variable success. Though these observations are intriguing, a definite causal relationship cannot be commented upon, until prospective cohort studies demonstrate the causal association. The data derived from prospective studies would serve as a blueprint for integrating multi-omics into clinical decision-making. Utilization of multi-omics techniques would also enable evaluation of genetic and environmental influences on the functionality of the intestinal microbiome. Specific and targeted manipulation of microorganisms of interest may then be able to prevent or treat CeD.

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Part V

Microorganisms in Pathogenesis and Management of Autoimmune Blood and Blood Vessel Disorders

16 Microorganisms in Pathogenesis and Management of Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

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Abstract

ANCA-associated vasculitis (AAV) is characterized by granulomatous and neutrophilic tissue inflammation, and is commonly accompanied with the development of antibodies that target neutrophil antigens. The two major antigens targeted by ANCAs are leukocyte proteinase 3 (PR3) and myeloperoxidase (MPO). The development of AAV has been linked to a number of potential risk aspects, including ecological, pharmacological, and microbial exposures. Infectious (microbial) factors are thought towards show a part in many types of vasculitis by causing inflammation of vessel walls as a result of direct or contiguous infection, type II or immune complex-mediated reaction, cell mediated allergic reaction, or inflammation caused by immune dysregulation triggered by bacterial toxin and/or super antigen production. Because immune suppressive

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medication in the absence of antimicrobial therapy may enhance morbidity while failing to resolve infection-related vascular inflammation, infectious entities should be considered as a potential inciting factor in vasculitis disorders. Therefore, amid these factors, here we contribute new consideration on infectious factors associated vasculitis.

Keywords

ANCA-associated vasculitis (AAV) · Proteinase 3 · Myeloperoxidase · Bacterial toxin · Superantigens

16.1 Introduction

The human body is constantly inhabited and interacted with vast number of microorganisms including bacteria, viruses, and fungi. These interactions may be commensalistic, mutualistic, or pathogenic. Numerous microbes can colonize variety of anatomical regions of human body including skin, mucous membrane, respiratory tract, gastrointestinal tract (GIT), mammary glands, and urogenital regions. The communities of commensalistic, mutualistic, and pathogenic microbes in human system are collectively referred to as human microbiome (Ogunrinola et al. 2020). Advances in sequencing research and computational methods have prompted a more extensive investigation of the role of microbiomes in human health and disease over time (Manasson et al. 2020). As of these researches, it has been clearly known that the maintenance of beneficial microbiome is very crucial for human health while dysbiosis (loss of microbiome diversity) has been associated to different persistent inflammatory disorders together with autoimmune diseases (Konig 2020).

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are disorders marked by blood vessel inflammation, endothelial and tissue injury, a lack of immune deposits, and interaction with the detection of circulating ANCAs. There are three kinds of minor vessel vasculitis that have been identified: granulomatosis with polyangiitis (GPA—formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis polyangiitis (EGPA, formerly known as Churg-Strauss syndrome), which are caused by a loss of tolerance to neutrophil main granule proteins (MPO). These disorders collectively account for a substantial saddle of severe organ/life threatening worldwide and are of enormous clinical significance due to immense progress in scenario amid treatments (Richard et al. 2020). Therefore, in recent years extensive studies have been conducted on AAVs. This chapter aspires to elucidate and increase the awareness of infectious origin of vasculitis, the circumstances of the science, recapitulate the recent advances in classification, epidemiology, role of biotic and abiotic factors in pathogenesis and prophylaxis and to recognize facts on fissures and prospect research precendences in AAV.

16.2 Classification of AAVs

The American College of Rheumatology (ACR) released early classification criteria for AAV in 1990, which included numerous kinds of vasculitis; however, no comparable criteria for MPA were published. Furthermore, the ACR criteria have a low sensitivity for diagnosing vasculitis. The Chapel Hill Concensus Conference (CHCC) published a new classification method for AAV in 2012 based on the size of blood vessels involved in large, medium, and small vessel vasculitis (Fig. 16.1). An additional meeting of the CHCC group updated their original statement, dividing those syndromes that primarily affect small blood vessels into the ANCA group (GPA, MPA, and EGPA) and the immune complex assembly (for example, HSP and cryoglobulinemia), as well as replacing eponyms through different syndrome names such as Wegener's granulomatosis as GPA, Churg-Strauss Syndrome as EGPA, and HSP as IgA vasculitis (Kronbichler et al. 2020a, b).

16.3 Epidemiology of AAVs

Globally the epidemiological property of AAVs has been explored. The yearly occurrence and pervasiveness of AAV fluctuates based on the latitude in equally northern and southern hemispheres (Li et al. 2018). There are 200–400 cases per million persons, according to estimates. However, the prevalence of AAVs has increased over time, owing to advancements in ANCA testing, illness classification, and clinical identification (Mohammad 2020). With a yearly frequency range from 0.5 to 2.0 per million and a prevalence of 10–45 per million, EGPA is not as prevalent as GPA or MPA, and the gender dispersal is relatively comparable. A multinational population research performed in Paris declared that the AAV prevalence in individual of European descent was 104.7 per million. It remained double that of non-Europeans (52.5 per million) and also reported that the frequency of GPA in non-Europeans is less than that of MPA (Mahr et al. 2004). A recent research conducted in Scotland reported that the occurrence of AAV happening four dissimilar seasons including autumn, winter, spring and summer was 15.1 per million people/year and the average age remained 66 years (54% cases were female). Moreover, the occurrence of AAV (not MPA) remained completely linked with rurality and there was no variation noted in relation with seasonal changes (Aiyegbusi et al. 2021). In India, the presence of EGPA (87.5%; 7/8 cases) and MPA (91.3%; 21/23 cases) was reported. In case of GPA anti-PR3 was predominant in 87.5% (28/32) cases (Chauhan et al. 2020). In China, 60% of GPA patients have MPO-ANCA and in Japan 83% (including considerable percentages of GPA) of AAV cases were positive for MPO-ANCA (Salvadori and Tsalouchos 2018).

Later and future advancements in information on the hereditary foundation could clarify these topographical and ethnic contrasts and help us to a superior comprehension of the pathogenesis of this disorder.

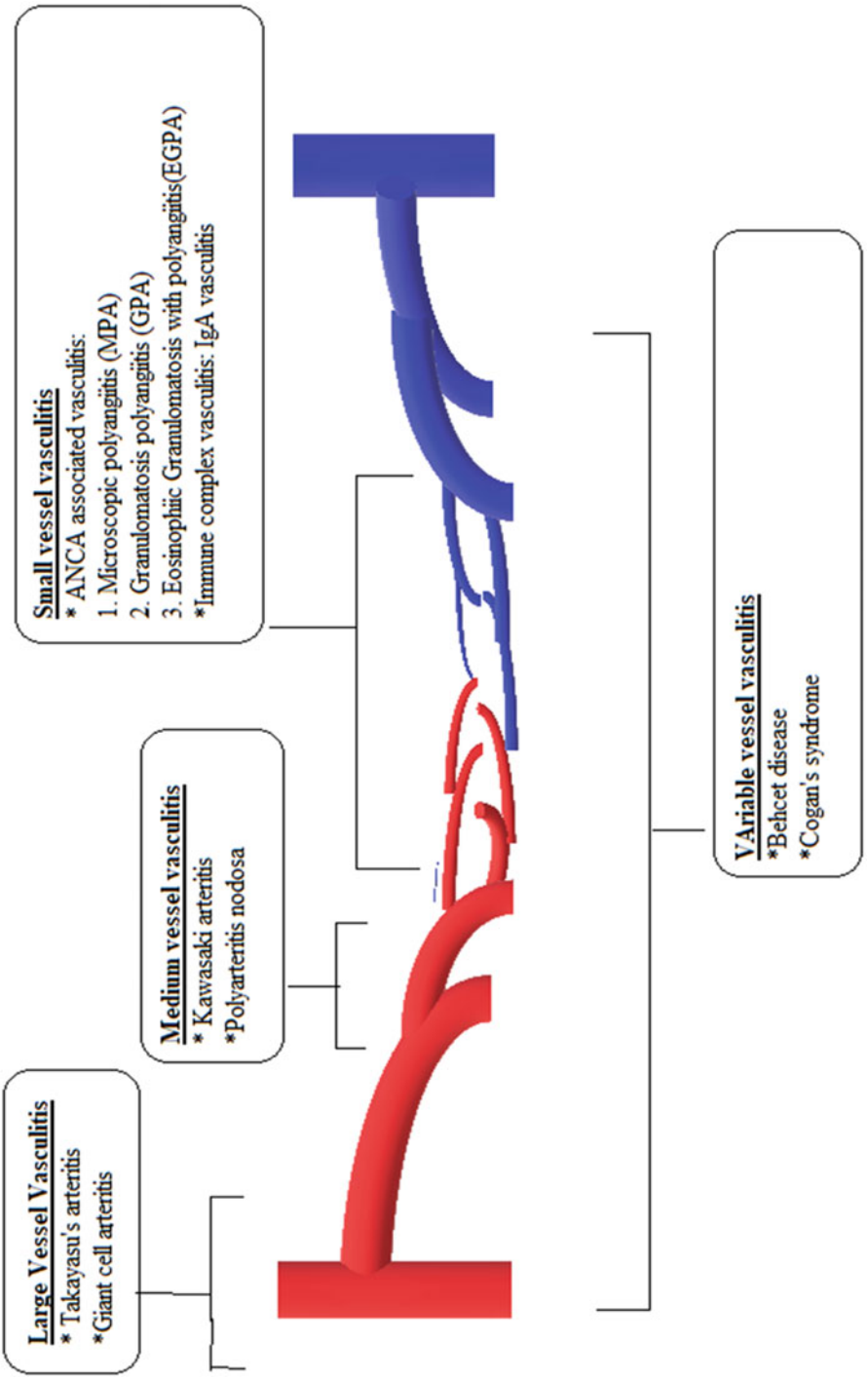

Fig. 16.1 Classification of AAVs according to CHCC

16.4 Microbial Pathogenesis of ANCA-Associated Vasculitis

AAVs have an unclear cause. Genetic factors have been proposed, however, they aren't very strong. In the etiology of AAVs, genetic and extrinsic factors appear to interact. Toxic chemicals, including silica exposure, have been implicated as extrinsic factors. Microbial variables, on the other hand, have received more attention in this study. Bacterial infections can cause the development of ANCA and other autoantibodies. Bacteria, such as *Streptococcus* sp., *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were the most common bacteria in our cohort followed by fungi and viruses and our rates of fungal and virus infections were greater and lower, respectively, than in prior studies (Table 16.1) (Yang et al. 2018).

Infections can produce vascular inflammation through two different mechanisms: through pathogen penetration of the vessel wall and immune-mediated damage to the vessel wall. Microorganisms can damage the wall directly by prompting smooth muscle cell (SMC) proliferation and relocation, as well as hindering SMC apoptosis; endothelial dysfunction (induction of procoagulants, hang-up of vessel dilation); and increased reactive oxygen species (ROS), cytokines, chemokines, and cellular adhesion molecules. Above alterations can be noticed in both atherosclerosis and vasculitis. Immune complexes, molecular mimicry, cytokine release, superantigens, ANCAs, autoantigen complementarity, and T cell mediated harm are all hypothesized pathways for microorganism-induced immune-mediated vascular injury (Rodríguez-Pla and Stone 2006). In the following, we have gone over each one in detail.

16.5 Cells and Pathways Involved in AAVs

16.5.1 Neutrophils

Neutrophil extracellular traps (NETs) produced by ANCA-stimulated neutrophils show a vibrant part in pathways important to vascular injury (Porges et al. 1994) and subsequent ANCA synthesis. As a result, the evidence implies that both inherited and epigenetic factors are involved in the complex etiology of ANCA-related vasculitis. Due to leukocytoclasis, neutrophils leave after a few days and are replaced by mononuclear leukocytes such macrophages, monocytes, and T lymphocytes. According to clinical observations and in vitro research, neutrophils appear to be important effector cells in the pathogenesis of human AAV. In vitro, ANCA can cause an oxidative burst, degranulation, inflammatory cytokine release, and endothelial cell damage in cytokine-primed neutrophils (Falk et al. 1990). *S. aureus* is a potent inducer of NETs. NETs are extracellular DNA and antimicrobial components secreted by neutrophils as part of their antimicrobial defense mechanism to limit bacterial transmission (Brinkmann et al. 2004).

Table 16.1 Microbial agents involved in AAVs

S. No	Etiological agent	Disease	Reference
1	Bacteria		
	Bordetella bronchiseptica	MPO-ANCA vasculitis	Ito and Uemura (2016)
	S. aureus	PR3-ANCA vasculitis	Kallenberg (2010)
	Group A Streptococci	*Streptococcus*-associated medium vessel vasculitis	Saad et al. (2021)
	Treponema pallidum	Rarely cause vasculitis	Guillevin (2004)
	Pseudomonas aeruginosa	Vessel thrombosis	Reich (1993)
	Legionella pneumophilia	Vessel thrombosis	Edelstein and Cutting (1986)
	E. coli	Vessel thrombosis	Stotka and Rupp (1991)
	Klebsiella sp.	Vessel thrombosis	Jang et al. (1992)
	Xanthomonas sp.	Vessel thrombosis	Harris et al. (1985)
	Aeromonas sp.		
2	Fungi		
	Candida sp.	Septic aortitis	Gornik and Creager (2008)
	Aspergillus sp.	Mycotic vasculitis	Fergie et al. (2000)
	Mucor sp.		
	Fusarium sp.		
	Coccidioides immitis		
3	Viruses		
	Hepatitis B virus (HBV)	HBV-associated Polyarteritis nodosa (HBV-PAN)	Teng and Chatham (2015)
	Hepatitis C virus (HCV)	HCV-cryoglobulinemic Vasculitis (HCV-CV)	Finkel et al. (1994)
	Cytomegalovirus (CMV)	CMV-induced vasculitis	McGoldrick et al. (2013)
	Varicella zoster virus (VZV)	GPA	Snider et al. (2014)
	Herpes simplex virus (HSV1 and HSV2)	HSV-associated vasculitis	Ziegler et al. (2013)
	Epstein–Barr Virus (EBV)	PAN	
	West Nile virus (WNV)	Cerebral vasculitis	
4	Rickettsia		
	Rickettsia rickettsi	Rickettsial vasculitis	Richards (2012)
	R. conorii		
5	Mycoplasma		
	Mycoplasma pneumoniae	Mycoplasma vasculitis	Dua et al. (2012)
6	Toxoplasma		
	Toxoplasma gondii	Taxoplasma vasculitis	Butler et al. (2013)

16.5.2 Lymphocytes (T and B Cells)

T cells are undeniably critical in the establishment of the ANCA autoimmune response, both through active B cell help and inadequate inhibition of the autoimmune ANCA response by regulatory T cells (Tregs) (Lepse et al. 2011). AAV patients have both a disrupted suppressive Treg cells network and a higher occurrence of a unique pro-inflammatory effector T cell subset (Free et al. 2013). ANCA causes glomerular neutrophil infiltration and MPO deposition, according to Kitchen and Holdsworth's study group (Ruth et al. 2006; Ooi et al. 2012; Tan et al. 2013; Gan et al. 2016). Anti-MPO $CD4^+$ T cells then detect MPO in glomeruli as a planted antigen, exacerbating glomerular injury. The same group recently investigated the involvement of autoreactive MPO-specific $CD4^+$ T cells in additional mouse model of glomerulonephritis. They discovered that transferring epitope-specific MPO-specific $CD4^+$ T cells into immunodeficient Rag1 knockout mice induced focal necrotizing glomerulonephritis when glomerular MPO deposition was induced either by passive transfer of MPO-ANCA and LPS or by planting the MPO epitope conjugated to a murine anti-glomerular basement membrane monoclonal antibody. They came to the conclusion that ANCA-activated neutrophils not only produce damage but also deposit MPO in the glomeruli, allowing autoreactive anti-MPO $CD4^+$ T cells to play a role in the formation of glomerular lesions (Ooi et al. 2012). The model's relevance to human disease is underscored by the similarity of the pathogenic human MPO B cell epitope revealed by MPO-ANCA to the nephrogenic murine T cell MPO epitope. By affecting central thymic T cells or peripheral Treg cells (Tan et al. 2013), or generating tolerance to the nephrotoxic MPO peptide by nasal insufflation of the peptide, a similar research group revealed the role of T cells in the pathophysiology of their AAV model (Gan et al. 2016).

Both T and B lymphocytes play a role in the pathogenesis of ANCA-associated vasculitis. T cells can be found in vasculitic lesions and granulomas. The function of Treg cell subsets has been weakened, but circulating effector T cell populations have expanded and are permanently activated. T cells and dendritic cells (DCs) are abundant near the site of inflammation, and they are influenced by several cytokines that regulate the immune response (Wilde et al. 2010). During remission, T cells remain activated. The activation of B cells has been linked to the occurrence of illness (Popa et al. 1999). Throughout the dynamic stages of ANCA-associated vasculitis, B cell homeostasis is disrupted, with an increase of cluster of differentiation (CD) 38 and a drop in CD5 expression (Dumoitier et al. 2015). B cell activating factor is released by ANCA-activated neutrophils, followed by ANCA epitope spreading to form pathogenic antibodies, overexpression of ANCA autoantigen genes, and other phases leading to pathogenic ANCA manufacture by B cells and plasma cells (Jennette and Falk 2014a). The treatment of PR3- and MPO-ANCA vasculitis with rituximab, a monoclonal antibody directed against CD20-bearing cells has become a staple. Once again, pro-inflammatory cytokines and chemicals regulate B cell development and activation.

16.5.3 Complement

Complement activation had not been suspected as a major pathogenic factor until animal model experiments demonstrated a major role for complement in the pathogenesis of AAV due to the relative paucity of complement component deposition at sites of vascular inflammation and glomerulonephritis in AAV compared to the more extensive localization of complement at sites of inflammation induced by recognized forms of immune complex-mediated inflammation that were known to elicit. It was discovered that anti-MPO transfer induced NCGN. Complement depletion can totally inhibit IgG, and the accompaniment membrane assault complex C3d and factor B have been found in the lesion areas of AAV patients (Chen et al. 2009). Active AAV patients had higher plasma levels of C3a, C5a, soluble C5b-9, and factor Bb than remission AAV patients (Gou et al. 2013); plasma complement factor H, a regulator of the another complement beginning pathway, was knowingly lesser in AAV patients associated to remission AAV patients and standard controls, and plasma factor H levels were in reverse associated with mixing levels of C3a, C5a, and Sc5b-9, according to linked with mixing levels of C3, C5 activation and C5a receptor (C5aR) engagement on neutrophils must be key actions in the development of ANCA illness.

Neutrophils stimulated by ANCA release components that trigger the other complement pathway, which produces C5a, a neutrophil chemoattractant. C5a also prepares incoming neutrophils for ANCA stimulation. Activated neutrophils adhere to and penetrate vessel walls, producing toxic oxygen radicals and destructive enzymes that cause apoptosis and necrosis in the neutrophils as well as adjacent vessel wall cells and matrix.

16.5.4 Cytokines and Chemokines

According to clinical and experimental results, pro-inflammatory stimuli, such as those generated by infections, appear to be a synergistic component in the onset, recurrence, and exacerbation of AAV. AAV is more likely to arise and relapse in the winter and spring, when infections are more common (Tidman et al. 1998a, b). Anti-MPO IgG causes a respiratory burst of murine neutrophils more effectively in vitro after priming with pro-inflammatory stimuli such as TNF-, LPS, or C5a (Falk et al. 1990; Schreiber et al. 2009; Hao et al. 2012; Huugen et al. 2005). To test the synergistic effect of pro-inflammatory stimuli in the anti-MPO IgG-induced NCGN animal model, wild-type mice were injected with bacterial LPS as a pro-inflammatory stimulus combined with anti-MPO antibodies (Huugen et al. 2005). Anti-MPO mice with LPS had more severe anti-MPO-induced NCGN and exhibited greater levels of circulating TNF- than anti-MPO mice without LPS. Anti-TNF therapy delayed the course of LPS-induced anti-MPO IgG-induced glomerulonephritis.

16.6 Major Steps Involved in AAVs

An autoimmune response or dysregulation of genomic expression of autoantigens occurs when a stimulus (infection or drug) is combined with insufficient immune control and/or suppression, resulting in vascular inflammation (Jennette and Falk 2014b). Several bacteria have been associated to the development of ANCA vasculitis, including *Staphylococcus aureus* (Table 16.1). An immune response to autoantigen complementary peptide structures is thought to exist in patients with genetically modified human leukocyte antigen-binding sites that recognize these complementary proteins. The pathogenesis of ANCA vasculitis is described in detail below and illustrated in Fig. 16.2.

16.6.1 Priming of Neutrophils and Monocytes

One of the most important aspects of the pathophysiology of ANCA-associated vasculitis is neutrophil priming, which leads to ANCA expression on the cell membrane. Systemic or tissue-specific pro-inflammatory stimuli activate this process. In both disorders (PR3- and MPO-ANCA vasculitis), many stimuli such as TNF-α (Falk et al. 1990), C5a (Schreiber et al. 2009), IL-1 (Noronha et al. 1993), IL-2R (CD25) (Berti et al. 2015), IL-6 (Wilde et al. 2014), IL-18 (Hewins et al. 2006), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) (Hellmich et al. 2000), high-mobility-group-protein B1 (HMGB1), and macrophage relocation inhibitory factor (MIF) are raised in contrast to controls. In PR3-ANCA vasculitis, higher levels of ADAM metallopeptidase domain 17 (ADAM17) and 1-trypsin polymers (Morris et al. 2011) have been described, while the expression of ADAM17 in MPO-ANCA vasculitis has yet to be investigated. In ANCA-associated vasculitis; however, CD122 (IL-2R) appearance on $CD4^+$ T cells is suppressed (Berti et al. 2015). The significance of monocytes in the complex pathophysiology has recently been reaffirmed (Brunini et al. 2016). In PR3-ANCA vasculitis, improved appearance levels of TNF-α, interferon-γ (IFN-γ) (Lúdvíksson et al. 1998; Csernok et al. 1999), and ADAM17, all of which have been linked to monocyte priming and are partly consistent of Th1 participation.

16.6.2 Activation of Neutrophils and Monocytes

Several factors are involved in neutrophil and monocyte activation during the vasculitic process. Among these cues, the complement system as a systemic stimulation and monocyte chemoattractant protein-1 (MCP-1) at the site of inflammation appeared to be central (Lindner et al. 2012). IL-8, one of the most important neutrophil chemotactic factors, has the ability to attract and activate neutrophils, potentially increasing neutrophil-mediated damage (Berti et al. 2018). MCP-1 is moreover implicated in the enrolment of monocytes and macrophages to the place of

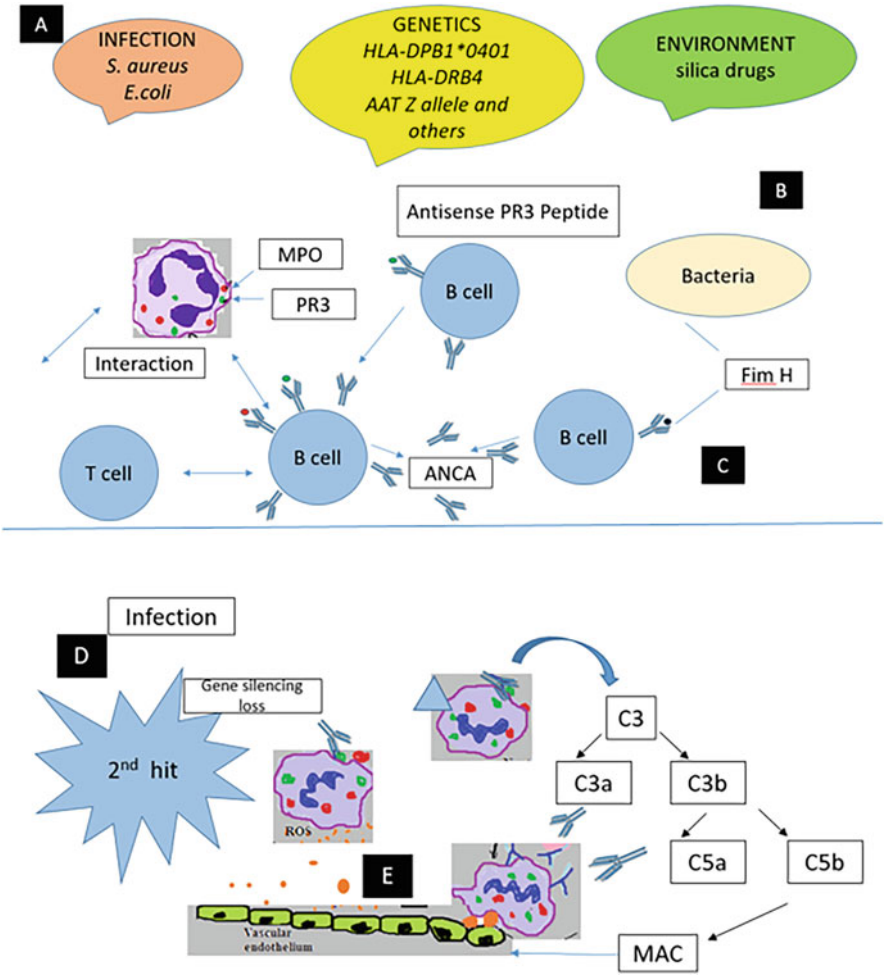

Fig. 16.2 Overview of pathogenesis of AAV. (a) Infectious, genetic, and ecological hazard issues have been linked to the exposure of cytoplasmic proteins in neutrophils (e.g., Proteinase 3 and Lysosome-associated membrane protein 2), and the subsequent formation of autoantibodies after communication with T and B lymphocytes. (b) Autoantibodies can also be produced against a complementary epitope to the autoantigen, such as anti-sense Proteinase 3 or through molecular mimicry, as in the case of the bacterial adhesion protein FimH. (c) Disease is frequently triggered by a second event, such as infection or the loss of gene silence. (d) Neutrophil activation produced by anti-neutrophil cytoplasmic antibodies too triggers the substitute complement pathway. (e) Anti-neutrophil cytoplasmic antibodies mediate endothelial damage in adding to complement-mediated microvascular injury by promoting neutrophil-endothelial cell contacts and cumulative neutrophil degranulation of cytotoxic chemicals and chemoattractants. *PR3* proteinase 3, *LAMP-2* lysosome-associated membrane protein 2, *FimH* enterobacterial fimbriae subunit

inflammation (Casselman et al. 1995) and multiple investigations have shown that urinary MCP-1 levels are too high in PR3-ANCA and MPO-ANCA vasculitis (Lindner et al. 2012). Avacopan, an oral C5a receptor inhibitor, has been proven to decrease urinary MCP-1 relatively faster than steroids (Jayne et al. 2017). As a result, urinary MCP-1 could be used as a biomarker to track illness progression. Besides its suggested anti-inflammatory characteristics, urinary soluble CD163 (sCD163), which is shed by monocytes and macrophages, is considerably enhanced in cases through illness and could remain a measure of macrophage/monocyte activity (Moran et al. 2020; Gaeggeler et al. 2005). Soluble Fats (Seino et al. 1998), which is raised in PR3-ANCA vasculitis, also act as a chemoattractant. In addition, both entities have higher amounts of IL-1β, IL-6, and the thymus and activation-regulated chemokine (TARC) (Berti et al. 2018). TNF-α, thromboxane A2 (TXA2), and CD14 (Tarzi et al. 2015) levels were higher in PR3-ANCA vasculitis; whereas C-C motif chemokine receptor 8 (CCR8) heights were developed and IL-10 expression was inferior in MPO-ANCA vasculitis. Complement factors C3 and C5 are amplified by MPO or ROS produced through neutrophil degranulation (Vogt 1996; Brilland et al. 2020). ANCA-activated neutrophils also maintain complement C3 stimulation and cleavage into C3a and C3b (Xiao et al. 2007), which is seen in both disease states. The C3 convertase of the another accompaniment pathway, C3bBbP, is overexpressed in patients with PR3-ANCA vasculitis. C5a, on the other hand, can prime neutrophils and promote ANCA-induced neutrophil activation since complement receptors are found in neutrophils (Schreiber et al. 2009). As a result, neutrophils are intimately linked to complement activation. There has been a documented differential expression pattern among interleukins, with PR3-ANCA vasculitis linked to elevated IL-10 and IL-32 (Popa et al. 2002; Csernok et al. 2008). IL-17A and IL-23, on either hand, are upregulated in both PR3-ANCA and MPO-ANCA vasculitis (Hoshino et al. 2008; Nogueira et al. 2010). PR3-ANCA binds tightly to membrane-bound PR3 provided by CD177 in PR3-ANCA vasculitis (Choi et al. 2010). CD177 expression is required for enhanced PR3 membrane expression, but it is not connected to circulating *PR3* or *PR3* gene transcription (Rees et al. 2003). Semaphorin 4D (SEMA4D) acts as a negative regulator of neutrophil activation, and SEMA4D proteolytic cleavage may promote neutrophil-mediated inflammatory responses (Nishide et al. 2017). MIF and matrix metalloproteinase 9 (MMP9) which regulate monocyte and T cell, access to the vascular wall (Watanabe et al. 2018), and are elevated in both illnesses; whereas CD14 is impacted in monocyte and neutrophil activation in PR3-ANCA vasculitis (Hattar et al. 2005).

16.6.3 T cell Activation

The recruitment of T cells is crucial in the development of vasculitis (Von Borstel et al. 2018). Th17 effector cells have been attributed to the pathogenesis of ANCA-related vasculitis (Dolff et al. 2019) and have been found to influence cytokine levels (Tesmer et al. 2008). IL-17A and IL-21 are affected by Th17 effector cells in ANCA-

associated vasculitis, with increased IL-17A levels in PR3-ANCA vasculitis and raised IL-17A levels in MPO-ANCA vasculitis. The levels of IL-18 and its binding protein (bp) IL-18bp are normally balanced, but an imbalance was found in numerous serious disorders (Dinarello et al. 2013; Lokau et al. 2016). IL-18 and IL-18bp levels were higher when associated to controls. ADAM17 and ADAM10 cleave the IL-6 receptor (IL-6R), resulting in a soluble (sIL-6R) form that was increased in both illnesses and had an unclear physiologic function (Lokau et al. 2016). Furthermore, soluble IL-6 concentrations associate by PR3-ANCA titers at baseline and cumulative attentions throughout remission are linked to illness deterioration in rituximab-treated patients (Berti et al. 2019). In PR3-ANCA vasculitis, soluble IL-2R and soluble CD30 levels are increased. IL-23, TARC, and osteopontin, a basic molecule, humoral factor, and cytokine (Icer and Gezmen-Karadag 2018), were upregulated in both conditions. The function of Th1 and Th2 effector cells were also disrupted. Th1 cells were overexpressed in ANCA-associated vasculitis, and a higher Th1/Th2 ratio was linked to higher IFN-expression in the kidneys during acute phases of the disease (Masutani et al. 2003). In ANCA-associated vasculitis, a reduction in CD28, a co-stimulatory signal was observed that favors the Th2 differentiation, and enhances Th1 polarization (Martinez Valenzuela et al. 2019). IFN-γ and IgG3 (the most potent immunoglobulin subclass) which trigger neutrophil activation, are secreted and induced by Th1 effector cells. During remission, this impact reverses, through a separation to Th2 response. Patients in reduction have more Th2 cells in their peripheral blood and less IFN-γ in their PBMC supernatant (Szczeklik et al. 2017).

16.6.4 B cell Activation

ANCA-activated neutrophils activate B cells, which leads to an increase in ANCA synthesis. B-lymphocyte stimulator (BLyS), also known as BAFF, is vital for B cell production and lifespan, as well as enhancing antibody-producing cells. PR3- and MPO-ANCA vasculitis are associated to high levels of BAFF in the blood. BAFF levels were also shown to be greater in a range of B cell-driven autoimmune diseases. BAFF levels were also higher in rituximab-treated patients (Holden et al. 2011), highlighting the importance of BAFF in B cell regeneration and antibody production. B cells can reduce Treg cell anti-inflammatory movement and speed up the growth of effector T cells by secreting IL-6 and TNF- (Eriksson et al. 2012). CD93, a receptor expressed throughout early B cell development, has risen in both entities (Chevrier et al. 2009). As previously mentioned, TARC levels are elevated in ANCA-associated vasculitis. Furthermore, B cell-attracting chemokine 1 (BCA-1) is a B lymphocyte-specific attractant that is increased in both illnesses (Jenh et al. 2001).

16.6.5 Tissue Damage and Repair

Both illnesses have the potential to harm a variety of organ systems, notably PR3-ANCA vasculitis. Several indicators associated with tissue injury and healing have

been discovered to be dysregulated. Nerve growth factor (NGF) and kidney injury molecule-1 (KIM-1) levels are higher in these circumstances, which are linked to inflammatory disorders (Monach et al. 2013). Matrix protein production, remodeling, and destruction are aided by MMPs and tissue inhibitors of metalloproteinase (Wang 2005). As a result, in PR3-ANCA and MPO-ANCA vasculitis, important components such MMP-3, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1 are increased (Monach et al. 2013). Transketolase (TKT), an enzyme engaged in the non-oxidative group of the pentose phosphate pathway (Alexander-Kaufman and Harper 2009), and tenascin C (TNC), an extracellular matrix protein involved in a variety of functions including cell adhesion, cell signaling, and gene expression (Midwood et al. 2016), were both elevated. Both groups had decreased levels of platelet derived growth factor-AB (PDGF-AB), which is involved in cellular migration, proliferation, and extracellular matrix protein formation, as well as the synthesis of inflammatory mediators (van Roeyen et al. 2012).

16.6.6 Endothelial Injury and Repair

Endothelial damage is caused by active vasculitis, which prompts endothelial repair mechanisms. The production of ROS, the formation of NETs, and local changes are thought to include some upstream mechanisms. These modifications could also explain why individuals with ANCA-associated vasculitis have a high rate of venous thromboembolic events (Kronbichler et al. 2019, 2017). PR3-ANCA, and to a lesser extent MPO-ANCA, cause monocytes to release soluble Fms-like tyrosine kinase-1 (sFlt1), which inhibits endothelium repair (Le Roux et al. 2012). One of the important players in these processes is intercellular bond molecule 1 (ICAM-1), which has been revealed to be upregulated in an inflammatory environment (Shan et al. 2004). Neutrophil gelatinase-associated lipocalin (NGAL), a protein released by a range of cell types and regulated in a variety of events such as inflammation, ischemia, and infection (Moschen et al. 2017), is higher in both entities. Only endothelial cells express E-selectin, and pro-inflammatory stimuli cause additional E-selectin to be produced, as demonstrated in PR3-ANCA and MPO-ANCA vasculitis. IL-6 is a potent pro-inflammatory cytokine that influences a variety of biological processes including apoptosis, survival, proliferation, and angiogenesis. Clusterin (apolipoprotein J), a widely expressed glycoprotein with cytoprotective properties (Koller et al. 2017), is upregulated in diseases. To tame endothelial lesions caused by active vasculitis, neo-angiogenesis is required. Lrg1, a leucine-rich alpha-2-glycoprotein, that facilitates angiogenesis and is mitogenic to endothelial cells (Wang et al. 2013), altered in ANCA-associated vasculitis. Because the S100A8/A9 protein (calprotectin) can cause pro-inflammatory replies in endothelial cells, it is increased in together illnesses (Pepper et al. 2017). Vasculitides are linked to an increased frequency of cardiovascular events when compared to a matched general population (Kronbichler et al. 2020a, b). An improper regulation of the IL-33/soluble suppression of tumorigenesis 2 (sST2) pathways could be one pathogenic

stage leading to atherosclerosis (Aimo et al. 2018). PAI-1, a protein that protects endothelial cells from apoptosis and death, was found to be decreased in patients with PR3-ANCA and MPO-ANCA vasculitis.

16.6.7 Role of Proteinase-3

Dysregulation in addition hyperactivity of PR3 are important in the pathophysiology of GPA, which is linked to PR3-ANCA. In neutrophils from GPA patients, PR3 production was disrupted (Martin and Witko-Sarsat 2017), and developed quantities of neutrophils through considerable PR3 concentrations in the plasma membrane has been linked to a poor prognosis. CD18, CD11b, and CD177 (a neutrophil external protein) bind to PR3 with high affinity (Martin and Witko-Sarsat 2017; Jerke et al. 2017), and are all involved in PR3's cell surface localization. PR3 has four hydrophobic areas on its surface that help it insert into the plasma membrane. PR3 can bind phosphatidylserine thanks to this "hydrophobic patch," which is helped by phospholipid scramblase 1 (PLSCR1) (Martin and Witko-Sarsat 2017; Kantari et al. 2007). Gabillet et al. (2012) found that overexpression of PR3 on apoptotic neutrophils slows macrophage efferocytosis, and GPA is linked to a change in the position of PR3-binding proteins implicated in apoptosis, such as annexin-A1, phospholipid scramblase 1, and calreticulin (Millet et al. 2015); Everts-Graber et al. (2019). PR3 attaches to inflammatory microvesicles with high levels of phosphatidylserine, enhancing their inflammatory potential (Kronbichler et al. 2020a, b). Membrane PR3 activates macrophages and DCs by stimulating the release of cytokines through its enzymatic activity (Millet et al. 2015). Phosphatidylserine may act as a receptor for soluble PR3, causing the vasculitis to worsen. Higher PR3 antibody production also predicts relapse in rituximab-treated patients (van Dam et al. 2021). The fact that antibody synthesis can occur before the onset of vasculitis (Collins et al. 2019) highlights the PR3's importance.

16.7 Gut Microbial Dysbiosis in AAVs

Microbiomic descriptions are now available for patients with small, medium, and large vessel vasculitis. The majority of research has been on the microbiomes of the gastrointestinal tract, with a smaller number of studies focusing on the microbiomes of the nasal, pulmonary, and circulatory systems. The majority of published research is observational and cross-sectional. When compared to illness and/or healthy controls, vasculitis patients had lower microbial diversity in nasal, fecal, and vascular samples, indicating dysbiosis. The bacteria that predominate in people with vasculitis vary, but in active disease, harmful bacteria outnumber commensal microorganisms. Following vasculitis treatment and better disease activity, improvement or resolution of dysbiosis has been found in the few long term studies. Animal models have suggested that intestinal dysbiosis may play a role in the development of several autoimmune disorders (DeGruttola et al. 2016; Zeng et al. 2017; Shi and

Mu 2017). Although it has been shown that gut dysbiosis in glomerulonephritis mice models (with a prevalence of *Escherichia coli* or *Citrobacter rodentium*) can locally expand Th17 lymphocytes, which can then migrate to the kidney via a chemokine pathway involving C-C motif chemokine ligand 20 (CCL20) and C-C motif chemokine receptor 6 (CCR6) (Krebs et al. 2016). Patients with ANCA-related vasculitis develop necrotizing glomerulonephritis, which is maintained by Th17 cell infiltration, which may be pre-activated in the gut by a shift in microbial makeup. Reduced bacteria functioning and diversification, desperately poor epithelial barrier function, inflammation, and diminished Treg cells in the gut mucosa are all implicated to dysbiosis in autoimmune disorders (Liu et al. 2021).

Microbiome imbalance in genetically susceptible people could explain the role of the microbiome in vascular inflammation. Because there isn't much information on vascular dysbiosis, it's probable that inflammation is caused by the body's attempt to compensate for dysbiotic changes in other places, such as the gut or oral mucosa. Only Buhcet's disease showed altered microbiome among the vasculitides in saliva and feces (Coit et al. 2016), while the link between altered microbiome and vascular inflammation is still unknown.

Finally, the role of dysbiosis in immune response tuning has logic in vasculitides; however, the evidence is currently weaker. Furthermore, the complex nature of these disorders raises concerns about the basic district where dysbiosis can emerge. Alterations in the gut microbiota have been identified as the primary basis of immune system beginning in chronic autoimmune diseases. Because locations are sterile in nature, the most widely accepted theory is that effector cells might be aware and triggered in the gut after being exposed to microbial peptides, and then travel to those sterile locations, where they could trigger the inflammatory cascade via a molecular mimicry process.

16.8 Diagnosis of AAVs

The diagnosis of infection-associated vasculitis is simple when cutaneous indications of vasculitis appear during the course of a known or already confirmed infection. If there are other vasculitic features present, such as internal jugular phlebitis following *Fusobacterium necroforum* pharyngitis, diagnosis may be more challenging (Walker and Mattern 1980). When no active infection has previously been discovered, two steps are required: (1) establishing a diagnosis of vasculitis and (2) identifying the likely causal organism. The identification of the organism is crucial to the antimicrobial therapy's efficacy. The framework of diagnosis of AAVs is shown in Fig. 16.3.

The simplest technique to identify the causative organisms is to examine materials, such as swabs of ulcers or other potentially ill sites or skin biopsy, using the suitable staining, at the very least Gram and Ziehl-Neelsen stains. When vasculitis is caused by bacteria, fungi, or parasites directly invading the artery walls, blood cultures provide positive results in 50% of cases (Asano et al. 2016). The Gram stain of infected person sputum sample revealed the presence of gram-negative

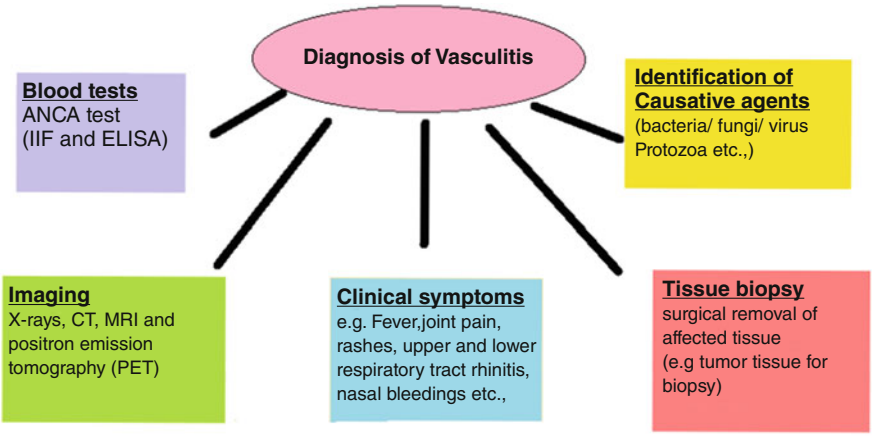

Fig. 16.3 Framework of diagnosis of AAV

coccobacilli *B. bronchiseptica*, suggesting the traditional method of preliminary identification of the etiological agent that was responsible for infectious vasculitis (Ito and Uemura 2016). Serological testing for various viruses, including HBV, HCV, and HIV, should be done on a regular basis. Using polymerase chain reaction (PCR) for viral nucleotides, the viral load of HBV or HCV3 infections, as well as Coxsackie viruses, VZV, CMV, or *Bartonella* infections, has been demonstrated and quantified (Gilden et al. 2016; Singh et al. 2016; Joshi et al. 2017; Mine et al. 2017).

In patients with GCA, VZV antigen and VZV DNA have been found in sequential biopsy specimens. VZV serology must not be conducted routinely because VZV is such a common and widespread virus. *B. henselae* was identified as the etiology of cerebral vasculitis using immunohistochemistry on a brain material. In mycoplasma-associated IgA vasculitis, antibody detection methods were used. In other series, viral particles or entire virions, as well as viral polynucleotides have been detected (Kuźma-Mroczkowska et al. 2015; Balakrishnan et al. 2016).

In maximum circumstances, the physician uses a series of tests to identify and classify the specific types of vasculitis. ANCAs interested in either leukocyte proteinase 3 (PR3) or myeloperoxidase, for example, distinguish granulomatosis with polyangiitis and microscopic polyangiitis (MPO). The diagnostic significance of ANCA is largely unquestionable. In clinical practice, these antibodies are differentiated using indirect immunofluorescence (IIF) and a variety of antigen-specific immunoassays, the most common of which are enzyme-linked immunosorbent tests (ELISAs). Antigen-capture techniques have improved, resulting in better assay enactment. In addition, a variety of other solid-phase antigen-specific assays can be employed to detect PR3-ANCA and MPO-ANCA (Bossuyt et al. 2017).

Even though ANCAs are more usually associated with AAVs, a positive ANCA test by IIF can occur in cystic fibrosis patients with microbial diseases such as tuberculosis and *Pseudomonas aeruginosa* infections (Weiner and Segelmark 2016). According to a recent study, enhanced NET synthesis caused by SARS

CoV-2 infection leads to AAVs via NETs due to excessive platelet, protein, and fibrinogen trapping (Yaqinuddin and Kashir 2020). The drug-associated AAV is linked to anti-lactoferrin and anti-neutrophil elastase antibodies in addition to MPO-ANCA. Azurocidin, bactericidal/permeability-increasing protein, and cathepsin G are proteins linked to a positive IIF ANCA test (Pendergraft and Niles 2014). Antigen-specific testing is not regularly conducted in AAV, and their clinical usefulness is unknown.

Patients with typical clinical manifestations such as fever, joint pain, upper and lower respiratory tract disease, kidney and other organ disease, and laboratory signs of inflammation (high ESR and C-reactive protein) are likely to have ANCA-associated vasculitis, even if the ANCA is negative or disappears during immunosuppressive treatments. GPA and MPA have some characteristics but differ in others. For example, ear, nose, and throat involvement is more likely in GPA than in MPA. Furthermore, patients with GPA typically have extravascular granulomatous lesions, which are not found in MPA patients (Moiseev and Novikov 2015).

Biopsy is not indicated for everyone with ANCA-related vasculitides, and histological testing results can be difficult to interpret. As a result, clinical equivalences of granulomatous inflammation, such as the following, should be considered: (1) lower respiratory tract and lung disease: persistent infiltrates, nodules, and cavities, bronchial stenosis; (2) upper respiratory tract disease: necrotising rhinitis with nasal bleedings and crusting, saddle nose deformity, chronic sinusitis (>3 months) and radiological damage, otitis media, and mastoiditis; subglottic stenosis of the trachea; (3) (Mueller et al. 2013; Moiseev and Novikov 2015).

16.9 General Treatment Methods

AAV patients exist with a varied range of disease activity. So, early diagnosis and treatments are needed for managing the disease and safety of an individual. The clinical and radiological symptoms, as well as microbiological features, were used to determine antimicrobial therapy. However, the treatment comprises an induction stage to achieve speedy rheostat of disease activity and maintenance phase for preventing relapses as well as the management of co-morbidities. Here, we focus on these components and discuss the recent updates regarding treatments.

16.9.1 Remission Induction

In most bacterial infections, treatment with appropriate antibiotics and/or surgical treatment can often stop the progression of inflammation and reduce ANCA titers to undetectable levels. The use of corticosteroids and immunosuppressants is based on histologic data rather than anti-infection therapeutic efficacy (Shi et al. 2020). However, high-dose GC has also been linked to negative metabolic consequences as mass advance and diabetes mellitus, as well as an increased risk of cardiovascular disease (Jayne 2021).

While GCs constitute the cornerstone of AAV treatment, mortality did not decline much until Cyclophosphamide (CYC) was added as a combination therapy. A 93% remission rate was achieved when CYC and GC treatment were combined. However, similar to GC, CYC has a significant treatment-related morbidity, and there has been an effort to reduce patient exposure (Carpenter et al. 2020).

In addition, Rituximab (RTX) is a monoclonal antibody that depletes the immune system's CD20-positive B cells. In 2016, RTX was added to therapy guidelines to help decrease the negative effects of CYC (Yates et al. 2016). Due to the expensive cost of RTX and the same prevalence of short-term treatment-related side effects, the CanVasc guidelines continue to suggest CYC as the preferred treatment for AAV.

Inhibiting the alternative complement pathway component C5a is intriguing in the treatment of AAVs because of its role in neutrophil activation and migration, as well as engagement of other inflammatory and thrombotic pathways. Two C5a inhibitors in clinical development for ANCA vasculitis include Avacopan, an oral C5a receptor inhibitor that has shown efficacy, safety, and steroid sparing in two Phase II trials, and IFX-1, a monoclonal antibody to C5a that is entering Phase II development (Jayne 2019). However, more research is needed to prove safety, particularly in terms of infectious risk, and the ability to replace steroids, as well as to look at if it can help with relapse prevention.

In addition to the above medications, because the course of AAV disease usually necessitates longstanding immunosuppression, mycophenolate takes also been investigated as a potentially less harmful alternative to cyclophosphamide and azathioprine. Plasma exchange (PLEX) in addition to normal immunosuppressive treatment is still contentious.

The use of intravenous immunoglobulins (IVIGs) to treat ANCA-associated vasculitis is based on a randomized controlled trial that encompassed a 3-month treatment cycle and follow-up period, as well as numerous case reports (Jayne et al. 2000). IVIGs are suggested as adjuvant treatment for ANCA-associated vasculitis, according to current EULAR guidelines, especially, if there is considerable residual disease activity despite exhaustion of the above-mentioned therapeutic options (Marvisi et al. 2020).

Trimethoprim-sulfamethoxazole (TMP-SMX; Co-Trimoxazole) is basically an antimicrobial agent used in AAV management for *Pneumocystis jirovecii* (PCJ) prophylaxis may also have a role as an effective induction monotherapy (2×960 mg/day) in GPA patients with AAV limited to the upper airway (i.e., locoregional GPA). TMP-SMX mechanism of action in GPA remains uncertain at this time. However, anti-inflammatory and/or anti-carrier mechanisms for *Staphylococcus aureus* have been proposed. Hence, TMP-SMX is an intriguing therapy for this population because of its low toxicity profile (Tervaert 2018).

Methotrexate is another vasculitis treatment that can be given orally or subcutaneously at a dose of 0.3 mg/kg/week. If clinical and biological tolerance is satisfactory, the dose may be increased to 20 and then 25 mg/week, reaching this level after 4–6 weeks, and then maintained until the treatment is completed. A folic acid supplement (preferable to folinic acid, which is more expensive) at a dose of

10 mg/week, 48 h after taking methotrexate, is essential to reduce possible toxicity, notably mucosal and hepatic toxicity, and to improve therapeutic maintenance.

16.9.2 Maintenance Therapy and Relapse Prevention

Re-evaluation of vasculitis, including testing for indicators of activity, is required after induction treatment to avoid going to maintenance treatment while the vasculitis is still active. Several drugs have been shown to be useful in the maintenance therapy; however, only a few may be used alone, and the majority must be combined with low-dose GC (Yates et al. 2016). The Steroid Tapering in ANCA vasculitis Evaluation Study conducted a meta-analysis of the length of GC maintenance medication and the rate of relapse (STAVE). The need of performing randomized control trials to determine the ideal GC maintenance time is demonstrated by the STAVE study (Rodrigues et al. 2017). The best drug for preventing relapse has yet to be determined. In a large, prospective, randomized, and controlled trial, the French vasculitis study group compared the use of methotrexate and azathioprine for maintenance therapy of ANCA-associated vasculitis after induction of remission with cyclophosphamide and corticosteroids. They found that methotrexate has no advantage over azathioprine in preventing relapse in ANCA-associated vasculitis, and it may (Gaber et al. 2008).

To lessen the danger of relapse and its repercussions, RTX is increasingly being utilized to maintain remission in patients with AAV. Dosing with RTX at a fixed interval of 500 or 1000 mg every 6 months for 2 years is recommended. After RTX cessation, there is a chance of relapse, thus patients should be closely followed (Tieu et al. 2020).

TMP-SMX has also been shown to be effective in maintenance therapy at higher doses than in PCJ prophylaxis, which is similar to its role in induction therapy. It was supported by the reports of Stegeman et al. (1996) who conducted a randomized controlled study (RCT) in GPA in September 1990, looking at the effects of maintenance trimethoprim–sulfamethoxazole (2×960 mg/day for 24 months) therapy (Stegeman et al. 1996).

16.9.3 Following Up and Withdrawing Therapy

At this point, the goal is to gradually lower the medications while maintaining the disease control. An infection can cause a relapse in some kinds of vasculitis (such as granulomatosis with polyangiitis). To prevent this, antimicrobial medications such co-trimoxazole may be prescribed. These medications can also aid to prevent against infection caused by heavier immunosuppressive drugs.

16.10 Role of Gut Microbes in AAVs Treatment

After colonization with normal microbiota, differentiation-suppressed myeloid and lymphoid progenitor cells in GF mice were reversed, demonstrating that gut microbiota enhances maturation of hematopoiesis (innate immunity) and lymphocytopoiesis (adaptive immunity) at both local and systemic levels (Khosravi et al. 2014). The mucus layer and epithelial layer of the gut barrier (which contain several junctional protein structures that regulate barrier integrity and paracellular permeability) serve as the interface between the host's internal environment and the outside world. As gut barrier function is disrupted, permeability to commensal microbes, microbial derived products (such as metabolites, virulence factors), and other luminal components increases, contributing to abnormal immune-inflammatory responses such as inflammation, allergy, and autoimmune disorders mediated by molecular mimicry and dysregulated T cell response. Interactions between the host and the gut flora influence the function of such physical and immunological barriers. The role of gut microbiota in the regulation of gastrointestinal T lymphocyte balance (Treg/TH17) ratio has been discovered, which is important in maintaining intestinal homeostasis and discriminating between pathogens and commensal microbes by organizing "immune tolerance-productive immune response" status. Numerous commensal microbes, such as *Bacteroides fragilis*, *Bifidobacterium infantis*, and Firmicutes, are responsible for the emergence of Treg cells, such as FOXP3-expressing Treg and anti-inflammatory IL-10-producing Treg lymphocytes, which are important in suppressing pathological inflammation caused by ectopic effector T cells and thus strengthening gut barrier activity (Lawley and Walker 2013).

16.11 Conclusion and Future Perspectives

AAVs are a category of illnesses that have some clinical characteristics and usually affect tiny veins. The relationship between infection and AAVs is a fascinating topic that has yet to be fully studied. Infections, vaccination, and antimicrobial medications have all been linked to AAV, and infections have been recorded during vasculitides and are thought to be trigger factors. There are cases where a single infection (e.g., HIV) can cause multiple forms of vasculitis and, conversely, where multiple microbes can cause the same vasculitic disease (PAN). Though, in mainstream of these cases, data comes from a small number of random case reports, making it impossible to draw a clear decision tying the infectious agent to AAVs etiology. Only a few cases have validated a causal connection between infection and vasculitis (HBV and HCV in PAN and cryoglobulinemia, respectively). The physiopathology of the intricate link between infection and AAVs is not totally known, but new molecular techniques could provide an improved information of the mechanisms behind these illnesses in the future, which could lead to a novel therapeutic approach, but the journey is still long.

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Microorganisms in the Pathogenesis and Management of Anti-phospholipid Syndrome (Hughes Syndrome)

17

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thrombosis and pregnancy complications in subjects with persistently positive antiphospholipid antibodies (aPLs). The clinical relevance of aPLs, including the increased risk of thrombosis in patients with anticardiolipin antibodies (aCLs), anti-β_2 glycoprotein I antibodies (anti-β_2GP1), and lupus anticoagulant (LA), is well known. Although aPLs are directly involved in the pathogenesis and are associated with the thrombotic risk, they happen infrequently, indicating that additional factors are required for this association. A "second hit" is also considered necessary to provoke clotting formation in aPLs carriers. Since the first report of APS, several microbial and viral agents have been shown to impact aPL generation and influence the clinical manifestations of APS. Different possible mechanisms have arisen to explain the production of aPL in the course of infections, including epitope spreading with β_2GP1 conformation modification, which expose cryptic epitopes, bystander activation, and molecular mimicry. However, limited attention has been paid to the mechanism sustaining chronic autoimmunity in APS. In recent years, many studies have emphasized the function of the microbiome in the pathogenesis of autoimmune diseases, including

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APS. Some of these potential mechanisms engaged in the pathogenesis of APS may have therapeutic implications.

Keywords

Antiphospholipid syndrome · Antiphospholipid antibodies · Hughes syndrome · Microorganisms · Infections

17.1 Introduction

Antiphospholipid syndrome (APS) is an autoimmune condition distinguished by the persistence of pathogenic autoantibodies targeted at membrane phospholipids and/or their linked plasma proteins. The annual incidence and prevalence have been described at around 2 and 50 per 100,000 persons, respectively (Duarte-García et al. 2019). The main characteristic of APS is the existence of persistent antiphospholipid antibodies (aPLs), which were described by Hughes et al. some decades ago (Hughes 1983), in the setting of arterial and venous thrombus and/or pregnancy loss. The Sapporo classification criteria of APS were revised in 2006 and are used as the main diagnostic guidelines. Patients are categorized as having APS when a clinical event happens (vascular thrombosis and/or pregnancy morbidity) along with the persistence of aPLs, such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β_2 glycoprotein I antibodies (anti-β_2GP1) (Miyakis et al. 2006). Other noncriteria aPLs like anti-phosphatidylserine/prothrombin (PS/PT) complex, anti-PT, anti-domain I of -β_2GP1 are also involved in APS (Sciascia et al. 2014). Catastrophic APS presents in less than 1% of all patients with APS and is characterized by multiple thromboses with high mortality (Asherson 1992). Although aPLs are closely associated with the pathogenesis of APS and are related to thrombosis, this event rarely occurs, indicating that other determinants are required to create thrombotic milieu. The "second-hit," which suggests activation of innate immunity, such as inflammation, infection, or surgery, is essential to precipitate the thrombotic event in aPL carriers (Meroni et al. 2018). Among the various mechanisms, infective agents may increase aPL exposure (van Os et al. 2011). Available data indicate that the production of aPLs induced by infections can be generated by multiple mechanisms involving epitope spreading, bystander activation, and molecular mimicry. The transient nature of aPL followed by infection may imply that continuous antigen exposure is necessary for the chronic perpetuation of autoreactive B-cell activation. Moreover, the microbiome has been implicated in the form of persistent self-antigens that either precipitate or prolong an autoreactive B-lymphocyte response (Chen et al. 2020). In this chapter, we review the role of microorganisms in the pathogenesis of APS and the therapeutic implications of these associations.

17.2 Origin and Development of Antiphospholipid Antibodies

β_2GP1 is a 50-kDa multidomain glycoprotein that circulates in the plasma and comprises 326 amino acids structured into five domains (DI-V), which are complement control proteins (CPP). Domains I-IV have been recognized in regulators of complement activation such as factor H, complement receptor I membrane cofactor protein (MCP), and decay-accelerating factors (DAF). On the other hand, DV embraces a phospholipid binding site and a region identified by aPLs. A relevant characteristic of all aPLs, and particularly highly pathogenic aPLs recognizing the R39-R49 epitope in the N-terminal domain I of β_2GP1, described as anti-DI antibodies, is that their recognition needs a conformational change of the antigen onto negatively charged surfaces or lipid membranes, throwing doubt on whether the epitopes identified by aPLs are cryptic in the β_2GP1 circulating form. In support of this perspective, structural studies have reported that β_2GP1 can assume alternative conformations (Agar et al. 2011).

Several pathogenic mechanisms have been proposed to describe the generation of aPLs, whose process is unclear, comprising an interplay between variants related to genetic predisposition and determinants related to the environment. Genetic predisposition to the development of aPLs (or APS) might produce some insights about the origin of these antibodies. Kambohl et al. made a genome-wide association study (GWAS) to analyze the susceptibility loci for the three major aPLs in patients with systemic lupus erythematosus (SLE) and controls. Although no single-nucleotide polymorphism (SNP) achieved the lower limit for genome-wide level of significance, many evocative genomic regions were described (Kamboh et al. 2013); particularly, the apolipoprotein H (*APOH*) gene, which is related to the occurrence of anti-β_2GP1. A second small GWAS demonstrated two loci related to the existence of anti-β_2GP1 that exceed the genome-wide level of significance: *B2GPI* and *MACROD2* (Müller-Calleja et al. 2016). Interestingly, the MACROD2 locus was found to have a relationship with anti-β_2GP1 in the previous GWAS (Kamboh et al. 2013). In spite of the fact that the mechanism by which this genetic locus may be implicated in the pathogenesis of APS is unknown, this genetic locus was reported as a risk factor for other autoimmune diseases (AD) (Ortiz-Fernández and Sawalha 2019). The delineation of the DNA methylation profile of APS may help to determine the basic molecular mechanism of the pathophysiology and disease continuation. Recently, 42 differentially methylated regions, 17 hypomethylated, and 25 hypermethylated, of which some were detected within the HLA region, were detected through a genome-wide DNA methylation evaluation of APS neutrophils. In APS patients, the most hypomethylated gene was *PTPN2*, which is a recognized genetic risk locus in many AD (Weeding et al. 2018). Moreover, hypomethylation within a single probe in the IFI44L promoter allowed differentiation of SLE from APS. Additionally, it has been found that methylation is decreased in the IL-8 promoter and higher in the F3 gene body in APS patients contrasted with healthy controls and associated with some clinical features (Patsouras et al. 2019). Likewise, the stimulation of human umbilical vein endothelial cells (HUVECs) with the combination of β_2GP1, anti-β_2GP1, and CXCL4 resulted in transcriptional

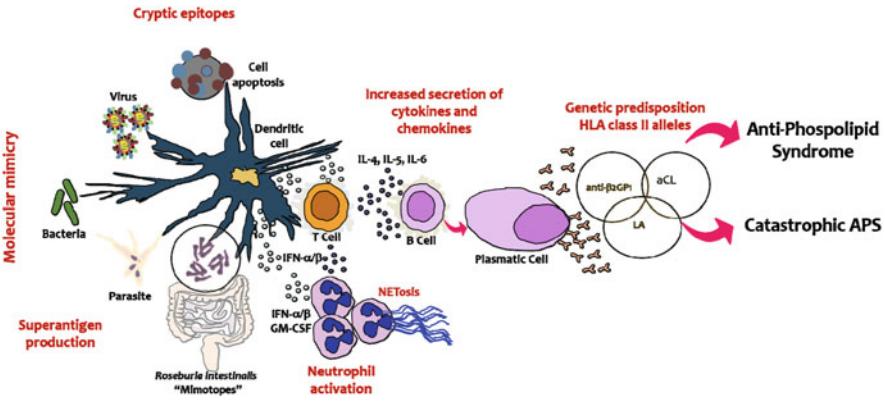

Fig. 17.1. Potential pathways responsible for the development of APS following infections. (Abbreviations: *aCL* anticardiolipin antibody, *anti-β_2GP1* anti-β_2 glycoprotein I antibodies, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IFN* interferon, *LA* lupus anticoagulant)

upregulation of epigenetic factors. These recent findings suggest that epigenetic disorders could be involved in the etiology of APS and may also have a role as diagnostic and therapeutic tools.

Several hypotheses for the understanding of the origin of aPL have been proposed: (1) the exhibition of the β_2GP1 cryptic epitope upon binding to oxidized surfaces and negatively charged surfaces (de Laat et al. 2011); (2) conformational changes that β_2GP1 present due to oxidative stress with oxidized aPLs, presenting neoepitopes that can lead to β_2GP1 antibody generation (Agar et al. 2011); and (3) apoptotic cell presenting β_2GP1 molecules via binding phosphatidylserine, displaying neoepitopes to the immune system (IS), and therefore leading to a breakdown of tolerance and leading to anti-β_2GP1 generation (Rauch et al. 2000).

Microbial pathogens may provoke the production of aPLs by antigen-dependent mechanisms such as molecular mimicry or induced in an antigen-independent manner, such as the breakdown of immune tolerance due to an inflammatory response. In multiple pathways, infectious agents can stimulate the host IS, which eventually leads to a loss of tolerance, autoantibody generation (Fig. 17.1), immune complex deposition, and finally, tissue damage. The most relevant mechanisms are molecular mimicry, superantigen generation, epitope spreading, bystander activation, modified apoptosis, clearance loss, epigenetic aspects, constant or periodic infection, and innate immunity activation with type 1 interferon (IFN) generation. Currently, the most relevant mechanism considered to explain the relationship between infections and clinical manifestations associated with aPLs in APS is molecular mimicry.

17.3 Infections and Antiphospholipid Antibodies

17.3.1 Infectious Agents and APS

It is widely recognized that AD, including APS, are probably the result of an altered immune response to infections. APS has been associated with several infectious, including hepatitis C virus (HCV) and HIV (Table 17.1). According to a systematic review and meta-analysis, analyzing different viral agents like HIV, HCV and human hepatitis B, both HIV and viral hepatitis are related to aPL positivity (Abdel-Wahab et al. 2016). Other viral infections possibly associated with APS are cytomegalovirus (CMV), Epstein–Barr virus (EPV), herpes simplex virus (HSV), and adenovirus (Abdel-Wahab et al. 2016). The occurrence of pathogenic aPLs have been shown during infections with parvovirus B19 (B19V), displaying an aPL IgG isotype and co-factor-dependent binding (Abdel-Wahab et al. 2018). An association between the B19VP1 unique region (VP1u) in the induction of APS has been reported (Lin et al. 2018). However, this relationship remains unclear, since aPL related to infections are not always associated with the increased risk of thrombosis and/or are found at low titers (Mendoza-Pinto et al. 2018; Palomo et al. 2003). Most cases of aPL associated with infections are temporally transitory, cofactor independent, and bind neutral or negative low-affinity aPL, while clinical events associated with APS are still considered an epiphenomenon (Martirosyan et al. 2019). Recently, a high frequency of LA has been reported in subjects with severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) (Bowles et al. 2020) during the recent COVID-19 pandemic. In this study, 44 (22%) out of 216 patients positive for SARS-Cov2 had LA, and most cases (90%) had prolonged activated partial-thromboplastin time (aPTT). In a more recent report, eight types of aPL antibodies in plasma (including anti-β_2GP1) were identified in 53% of hospitalized patients with COVID-19 (Zuo et al. 2020). In addition, a release of neutrophil extracellular traps (NETs) was related to elevated titers of aPL antibodies in these patients. When an experimental analysis was performed in the same study, the administration of IgG purified from COVID-19 patient serum into mice also induced venous thrombosis. Although thrombotic events are relatively frequent during acute SARS-CoV2 infections, and share clinical and laboratory features with hyperferritinemic syndrome (Colafrancesco et al. 2020), the appearance of aPL in critically ill COVID-19 subjects and their connection with thrombotic complications are rare and contradictory.

On the other hand, aPLs have been linked to several bacterial infections, such as *Coxiella burnetii*, *Helicobacter pylori*, *Mycoplasma pneumonia*, *Streptococci*, *Borrelia burgdorferi*, and *Mycobacterium tuberculosis* infections. However, these infections are not often related to clinical manifestations with thrombotic events. Interestingly, subjects with syphilis caused by *Treponema pallidum* show aCL antibodies, which might be provoked by the cross-reactivity of syphilis antibodies with treponemal cardiolipins (Pavoni et al. 2021). Patients with leprosy also present aPL positivity and β_2GP1-dependent binding (Mendoza-Pinto et al. 2018). According to one experiment in mice immunized with proteins derived from

Table 17.1 List of major microorganisms involved in aPL generation and thrombosis

Microorganism	aCL	Anti-β_2GP1	LA	Thrombosis
Viral infections				
Adenovirus	+	+	–	–
CMV	+	+	+	+
EBV	+	+	+	+
Hepatitis A	+	–	–	+
Hepatitis B	+	+	+	–
Hepatitis C	+	+	+	+
Hepatitis D	+	+	+	–
HIV	+	+	+	+
HTLV	+	+	–	–
Influenza A	+	–	–	+
Mumps	+	–	–	–
Parvovirus B19	+	+	+	+
Rubella	+	–	–	–
SARS-CoV-2 virus	+	+	+	+
Varicella zoster virus	+	+	+	+
Bacterial infections				
Borrelia burgdorferi	+	+	+	+
Chlamydiae	+	+	–	–
Coxiella burnetii	+	–	+	–
Escherichia coli	+	+	–	+
Fusobacterium necrophorum	+	–	+	+
Helicobacter pylori	+	+	–	–
Klebsiella spp.	+	–	–	–
Mycobacterium leprae	+	+	+	+
Mycobacterium tuberculosis	+	+	–	+
Mycoplasma pneumonia	+	+	–	+
Salmonella spp.	+	+	+	+
Staphylococcus spp.	+	–	–	+
Streptococcus spp.	+	+	+	+
Treponema pallidum	+	+	–	–
Parasitic infections				
Leptospira spp.	+	+	–	–
Leishmania	+	+	+	—
Plasmodium falciparum	+	–	–	–
Plasmodium malariae	+	+	–	+
Toxoplasmosis	+	–	–	–

[Note: adapted and modified from *Environmental Triggers of Autoreactive Response: Induction of Antiphospholipid Antibody Formation.* Available from https://www.frontiersin.org/articles/10.3389/fimmu.2019.01609/full. Review paper. Accessed June 23, 2021. Creative Commons Attribution 4.0 International Public License https://creativecommons.org/licenses/by/4.0/ (Martirosyan et al. 2019)]. (Abbreviations: *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HIV* human immunodeficiency virus, *HTLV* human T-lymphotrophic virus)

Haemophilus influenzae and *Neisseria gonorrhoeae*, bacterial peptides homologous with β_2GP1 induced pathogenic anti-β_2GP1 antibodies along with APS clinical features. There is less data about the role of parasitic or fungal infections inducing aPLs, which mostly occurs after *Plasmodium falciparum* and visceral leishmaniasis infections (Mendoza-Pinto et al. 2018).

17.3.2 Infections and Catastrophic APS (CAPS)

CAPS, also described as Asherson syndrome, is the most severe form of APS, with widespread intravascular thrombosis simultaneously leading to multiorgan failure. Histologically, CAPS is described as acute thrombotic microangiopathy. Currently, the international "CAPS registry," created in 2000 by the European Forum on Antiphospholipid Antibodies, provides insight about this condition. This registry collects data about the main clinical manifestations, laboratory tests, and treatments from 500 patients with CAPS. Interestingly, around 75% of patients from this registry demonstrated precipitating factors for CAPS, with infections being the most common (almost 50% of cases); other triggering events were malignancy and surgery (Rodríguez-Pintó et al. 2016). Similarly, infections are also a common precipitating factor for CAPS in children. According to a previous systematic review, the most frequent infectious factors for CAPS are bacterial pathogens, like *Shigella*, *E. coli*, *Klebsiella*, *Salmonella*, *Streptococcus*, *Staphylococcus*, and viruses such as HVC and the herpes family (Abdel-Wahab et al. 2016). Emergent infections such as Chikungunya virus, a single-stranded RNA mosquito-borne alphavirus of the Togaviridae family, have been involved in a few cases of CAPS (Betancur et al. 2016). A relationship between the severe form of COVID-19 and CAPS has been drawn. Both diseases share some characteristics: multiple organ failure, elevated cytokines, disseminated intravascular coagulation (DIC), thrombotic microangiopathy, and finally a higher mortality rate (Roncati et al. 2021). Although, aPLs and LA have been associated with severe COVID-19, there are also false-positive tests, and therefore, the interplay between aPLs and COVID-19 coagulopathy is controversial, and further analyses are needed (Favaloro et al. 2021).

Similarly to APS, the main possible pathogenetic mechanism that has been suggested to explain the interaction between infections and the presence of CAPS is molecular mimicry, in which a robust protein sequence homology between infections, mainly viruses and peptides of β2-GPI, has been proposed (Mendoza-Pinto et al. 2018). Aside from the initiator role of infections in CAPS, they are related to mortality in these patients (14.1%), which is due to sepsis, candidiasis, cerebral abscess, or pneumocystis-associated pneumonia (Rodríguez-Pintó et al. 2016).

17.4 Infectious Origin of Antiphospholipid Antibodies

17.4.1 The Role of Molecular Mimicry

Molecular mimicry is a phenomenon where a foreign element shares sequences or structural similarities with self-antigens. As a result, self-tolerance is interfered with and pathogen-dependent IS cross react with self-antigens. Evidence suggests a homology between proteins of microorganisms and peptides originated from β_2GP1, which contribute to T- and B-cell activation (Martirosyan et al. 2019). Different microorganisms secrete exotoxins (superantigens), which evolve to target subsets of T cells, activating them and augmenting the production of effector cytokines (e.g., INFγ) and chemokines that control the expression of MHC class I and class II molecules. In order to determine the potential pathogenic effect of infections, which exhibit surface components analogous to the major immunogenic epitopes targeted by anti-β_2GP1 antibodies, diverse animal model studies have been reported. Induced pathogenic aPLs, by in vivo binding of infectious agents such as β_2GP1 to self-anionic phospholipid, forms immune complexes directed at the aPLs produced (Gharavi et al. 1999). Blank et al. demonstrated, by in vitro and in vivo experiments, that synthetic peptides with a high homology with various domains of β_2GP1 reduced endothelial cell activation (ECA) and adhesion attributes of monocytes (Blank et al. 1999). This group also found that microbial pathogens conveying sequences linked to a hexapeptide (TLRVYK) are recognized by pathogenic anti-β_2GP1 antibodies. Following immunization, high titers of antipeptide anti-β_2GP1 antibodies were detected in mice immunized with *H. influenza*, *N. gonorrhoeae*, *Candida albicans*, and *tetanus toxoid* and that presented some APS features like thrombocytopenia, prolonged aPTT, and an increased risk of fetal loss, establishing a possible pathogenic mechanism of molecular mimicry in experimental APS (Blank et al. 2002). This evidence supports the concept that some viral and bacterial agents may contribute to an autoreactive aPL response through the interplay of peptides bound to phospholipids derived from infections with host-β_2GP1.

Conformational changes in β_2GP1 leading to anti-β_2GP1 antibody generation can be provoked by infections. Specifically, β_2GP1 was demonstrated to link with *Streptococcus pyogenes* surface protein H, and as a consequence, there is an aPL response derived from the exhibition of cryptic epitopes within domain I of β_2GP1, precipitating an aPL response (van Os et al. 2011). In addition, alterations in host antigenic components as a result of tissular damage and the production of neoepitopes may lead to molecular mimicry. The inflammatory response may contribute to modifications of protein structures, delivering a source of neoepitopes that may be identifiable by antibodies as non-self. Moreover, continuous exposure to β_2GP1-bound anionic surfaces with the presentation of the cryptic components may play a function in maintaining the anti-β_2GP1 antibody response in APS (Yamaguchi et al. 2007).

17.4.2 The Link Between Innate Immunity and APS

Innate immunity activation is also a crucial process that leads to autoimmunity. There is an interaction between viral nucleic acids and other pathogen- or damage-associated molecular patterns (PAMPS and DAMPs, respectively) with several pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and nucleotide binding and oligomerization domain receptors (NLRs).

Molecular patterns derived from microorganisms like lipopolysaccharides (LPS) are identified by TLR4 or TLR2 according to some studies. β_2GP1 is a scavenger of LPS. A synthesized peptide (LAFWKTDA) from domain V of β_2GP1, analyzed by surface plasma resonance, could compete for the binding of β_2GP1 to LPS (Ağar et al. 2011). The interaction between aPL binding and endothelial cells (EC) triggers the TLR4 transduction signal pathway, demonstrated by Raschi et al. It was exhibited by a transitory co-transfecting microvascular EC with dominant-negative constructs of various elements of the pathway (Delta TRAF2, Delta TRAF6, Delta MyD88) (Raschi et al. 2003). Specifically, it showed activation of myeloid differentiation factor 88 (MyD88), and phosphorylation of interleukin-1 receptor-associated kinase (IRAK), leading to a translocation of nuclear factor kappa B (NF-kB). Moreover, in vivo studies exhibited the pathogenic function of TLR4 in APS by analyzing thrombogenic aPL activity in LPS non-responsive mice and the interplay between *tlr*4 gene SNP and APS (Pierangeli et al. 2007). More recently, Mueller-Calleja et al. provided evidence that human monoclonal aPLs can facilitate the transcription of NLRP3 and caspase-1, leading to an activation of inflammasome specific for NLRP3 through endosomal NADPH-oxidase-2 (NOX2), eventually leading to the activation of mononuclear cells (Müller-Calleja et al. 2015).

Increased neutrophil activation, which plays a crucial part in thrombus formation, might be associated with APS, since the expression of cell adhesion genes and proteins like CD66, carcinoembryonic antigen-related cell adhesion molecule 1, and activated Mac-1 by neutrophils is increased in APS patients, resulting in higher neutrophil adhesiveness (Sule et al. 2020). Neutrophils from APS patients showed a proinflammatory signature with overexpression of IFN signaling genes. In vivo studies found that P-selectin glycoprotein ligand-1 (PSGL-1), which is a relevant adhesion molecule, has increased expression of neutrophils in APS patients (Knight et al. 2017). Moreover, a deficiency of PSGL-1 has been related to decreased leukocyte vessel wall adhesion and NET formation, while the infusion of wild-type (WT) neutrophils led to a restoration of the thrombosis phenotype in PSGL-1-deficient mice and an anti-PSGL-1 monoclonal antibody impeded APS IgG-mediated thrombosis in WT mice. Therefore, PSGL-1 might be a possible treatment target (Knight et al. 2017). Previously, neutrophils have been determined as a homogeneous population. However, recently, they are recognized to have heterogeneous and diverse functions. In order to distinguish neutrophils and their subsets, several strategies based on surface marker expression or density have been proposed (Sagiv et al. 2015). High-density neutrophils (HDNs), which were identified in both healthy and diseased subjects, and low-density neutrophils (LDNs), mostly reported in pathological states, were analyzed in APS. LDNs from

patients with APS revealed a primed or exhausted phenotype that might be a result of a pre-activation by aPLs, while HDN activation was relatively easy to provoke and showed greater NET generation in APS patients than controls (Mauracher et al. 2021). Similarly, recent evidence indicated that NET markers are augmented in pregnant women with APS, in whom defective deep placentation was influenced by NETs (Lu et al. 2020).

17.4.3 Commensal Microbiota in APS

Host–microbiota interactions are fundamental for the development of the IS. The microbiome is a potential source of persistent self-antigens that either precipitate or perpetuate an autoreactive B-cell response (Chen et al. 2020). The gut microbiome has been linked with APS, according to a recent study (Ruff et al. 2019), which highlighted the gut as a potential chronic trigger in patients with APS. Kriegel et al. demonstrated that *Roseburia intestinalis* contains amino acid sequences that are highly homologous to sequences (mimotopes) found in B-cell and T-cell epitopes within β_2GP1. Although the frequency of this commensal bacterium was comparable in individuals with anti-β_2GP1 antibodies (the major autoantigen in APS), individuals with APS and healthy controls, subjects with anti-β_2GP1 antibodies had signs of chronic subclinical intestinal inflammation and systemic adaptive immune responses to *R. intestinalis* (Ruff et al. 2019). Patients with APS had greater levels of antibodies that were cross-reactive within a bacterial DNA methyltransferase expressed by *R. intestinalis* compared with healthy individuals. In addition, levels of these antibodies correlated with levels of anti-β_2GP1 antibodies in patients with APS. Importantly, the oral administration of *R. intestinalis* in a mouse model of spontaneous APS triggered the development of anti-human-β_2GP1 antibodies, as well as APS-related morbidity and mortality. Together, these data support a role for non-orthologous commensal-host cross-reactivity in the development and persistence of autoimmunity in APS. Therefore, selecting patients who show reactivity to the bacterium and have predisposing genes will be essential to identify who could possibly benefit in the future from attempts to remove this and similar cross-reactive triggers from the gut. An experimental study using a spontaneous (NZWxBXSB)F1 model of APS/systemic lupus erythematous (SLE) demonstrated that depletion of the gut microbiota with a regimen that approximates a germ-free state in the gastrointestinal tract leads to lower anti-β_2GP1 titers and protection from thrombotic events in mice (Vieira et al. 2013).

17.4.4 Vaccines and APS

There is increased global interest in vaccination safety following various cases of possible post-vaccination effects related to autoimmune disorders. Causal relationships between different vaccines and autoimmune reactions have been reported in several studies, and influenza vaccination is the main one related to

aPL production (Mormile et al. 2004). In SLE patients, this vaccine may increase the probability of thrombotic events (Tarján et al. 2006). However, there is strong experimental evidence for post-vaccination generation of aPL with the tetanus toxoid vaccine, which triggers antibody production due to different adjuvants (Zivkovic et al. 2012). Undoubtedly, vaccines share molecular patterns with microorganisms to elicit an adequate immune response.

As previously mentioned, the presence of APLs has been reported in COVID-19 cases. Nevertheless, the association with the COVID-19 is unclear. After the beginning of the mass COVID-19 vaccination campaign, a possible link between COVID-19 vaccines and unexpected thromboembolic events was observed. At present, available COVID-19 vaccines include mRNA-based (BNT162b2 and mRNA-1273) and adenoviral vector-based (ChAdOx1-S and Ad26.COV2) formulations. There are reports of thrombocytopenia and thrombotic events similar to APS in recipients of either adenoviral vector or mRNA-based COVID-19 vaccines. Young women were the main group that developed severe coagulation disorders related to vaccination and also the group in which APS is most prevalent (Talotta and Robertson 2021).

Adenoviral vector-based vaccines can induce platelet destruction in the reticulo-endothelial system (Stone et al. 2007). A previous study described an in vitro aPTT elongation in recipients of recombinant adenoviral-vector serotype-35 HIV vaccine, related to the transient appearance of aPLs (Crank et al. 2016). A recent article described a small case series of patients who presented thrombotic events and thrombocytopenia after ChAdOx1-S vaccine application: those who died were strongly positive for anti-PF4 antibodies (Greinacher et al. 2021), and one patient was also positive for aPL. In silico and in vitro analyses indicate that anti-β_2GP1 antibodies selectively bind β_2GP1 that is complexed to PF4 (Sikara et al. 2010). These immunocomplexes can activate platelets through p38MAPK phosphorylation and the release of thromboxane B2. Therefore, it is possible that the binding of anti-β_2GP1 antibodies and their ligand reveals epitopes of PF4, inducing the production of anti-platelet PF4 antibodies. As a result, the sum of the effects of both anti-β_2GP1and anti-PF4 autoantibodies could increase the risk of thrombotic events.

The influence of COVID-19 mRNA-based vaccines on the coagulation system is unclear. Clinical trials revealed no concerns about this characteristic, but several reports demonstrate that extracellular RNA could activate coagulation factors (Nakazawa et al. 2005), conferring a prothrombotic state to platelets and endothelial cells.

mRNA and other ribonucleic acids, when they interact with PRR placed in target cells, may initiate a type I interferon response (Talotta 2021), which could be associated with the production of aPLs (Xourgia and Tektonidou 2019). Likewise, aPLs can induce an irregular immune response, which involves innate immune cells, monocytes, cytokines, activation of complement, and NETosis (Bravo-Barrera et al. 2017). For this, mRNA-based vaccines are highly immunogenic and may induce a pro-inflammatory state (second hit) and the production of APS in asymptomatic aPL-positive subjects.

Additionally, cellular vesicles that take part in endothelium and platelet interaction have a molecular resemblance to mRNA-based vaccines and are another possible explanation for the link between vaccination and thrombosis. In vitro human anti-β_2GP1 antibodies activate resting endothelial cells by the stimulation of the inflammasome platform assembly and the release of extracellular vesicles, including IL-1β (Wu et al. 2015). Finally, anti-β_2GP1 antibodies activate resting endothelial cells through a toll-like receptor 7 (TLR7)-mediated pathway, which is attributed partly to the release of certain microRNAs (Wu et al. 2015). Therefore, TLR7 may recognize mRNA from COVID-19 vaccines and other single-stranded RNA molecules (Fotin-Mleczek et al. 2011).

17.5 Therapeutic Implications

Increased understanding of the relationship between infections, APS and its catastrophic variant, or as a game-changer in disease severity and course is crucial for the development of alternative strategies for the treatment of APS. On the basis that infections and autoimmunity have in common the activation of pathogenic pathways, it is reasonable to investigate the use of antibiotics as either prevention or treatment, particularly in catastrophic APS, in addition to the regulation of microbial-induced immune responses, based on which mechanism may provoke disease progression like "hit and run," which leads to bystander activation or constant stimulation of the IS. The role of antimicrobial agents on APS has previously been described (Blank et al. 1998; Cicconi et al. 2001).

As previously stated, neutrophils, through NETs, are required for APS-potentiated thrombosis in APS models (Knight et al. 2017). Currently, there are novel therapeutic targets, such as surface adhesion molecules, identified thanks to profiling of APS neutrophils (Sule et al. 2020). Since new evidence suggests that second messenger cyclic AMP may suppress NET release in some conditions, a preclinical study researched the stimulation of surface adenosine receptors to trigger cyclic AMP formation in neutrophils to mitigate thrombotic events in APS (Ali et al. 2019).

Selective agonism of the adenosine A2A receptor (with CGS21680) may efficiently prevent aPL antibody-mediated NET release from control and APS neutrophils.

Given the recent evidence of the role of commensal microbiota in APS, reversing the negative effects mediated by the microbiota might alter the course of APS. For instance, in β_2GP1-immunized Balb/c mice, the intake of probiotics from fermented milk products decreased anti-β_2GP1 serum levels and shifted the immune response from Th2 to Th1 type (Amital et al. 2007).

Since thromboembolic events and DIC related to SARS-CoV-2 infection may show severe APS (Cavalli et al. 2020), some treatment approaches have been designed to control COVID-19 complications, such as thrombosis, including repurposed drugs directed at inflammation. This could motivate better approaches for the treatment of B-cell-dependent conditions. Potential drugs such as rituximab,

ocrelizumab, and anti-C5a monoclonal antibodies have received attention in this respect. The use of plasma exchange or intravenous immunoglobulin, apparently useful in some cases of APS and its catastrophic variant (Rodríguez-Pintó et al. 2019), warrants further consideration. Several drugs have been shown to have inhibitory effects on the TLR4 pathways, for example, TAK-242 (Resatorvid) or GLS-1027 R, which block NETs associated with thrombosis could be studied in the context of COVID-19 and related thrombosis (Plunk et al. 2020). Inhibitors of the mechanistic target of rapamycin (mTOR) with immunomodulatory and certain antiviral efficacy have shown some benefits in APS, and recent evidence shows that the in silico-designed chemotype (SF2523), targeting α/mTOR/BRD4, inhibits SARS-CoV2 infection (Acharya et al. 2021).

17.6 Conclusions

Infections are potential inducing factors for autoantibody production in APS. Several infectious agents have been related to the pathogenesis of APS and infections are potential triggers for autoantibody production in this context, but there is no definitive evidence. Proposed mechanisms involve molecular mimicry, enhanced release of cytokines and chemokines, selective activation or depletion of lymphocyte populations, neutrophil activation with NET generation, and exposure of cryptic epitopes due to cell death. Some infections may also affect the immunogenicity of β_2GP1 (increase in oxidized β_2GP1), which may function as a carrier of LPS, and the latter as a "second hit" for the pathogenic activity of the anti-β_2GP1 antibody may support the idea of infection as the trigger of APS in genetically predisposed individuals. Cross-reactivity among mimotopes present in gut microbiota and the major T-cell and B-cell autoepitopes of β_2GP1 may impact the mechanisms of tolerance of these immune cells, taking part in the progress and persistence of autoimmunity in APS.

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Microorganisms in Pathogenesis and Management of Behçet Disease (BD)

18

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Abstract

Behcet's disease or syndrome (BD/BS) is a disease that involves several systems and organs. The etiopathogenesis of BD is characterized by a complex interaction between genetic predisposition and microorganisms. The term microbiome refers to the constellations of the whole microorganisms (bacteria, viruses, and fungi) in the human body and their ecosystem. The alterations in the balance of microbiota's microorganisms are defined as "dysbiosis" and it can be a contributing cause of different immune diseases including BD. One of the mechanisms by which dysbiosis can probably lead to the triggering of a pro-inflammatory process is molecular mimicry. The diets rich in plant-based foods have positive effects on BD. In addition to the diet, the use of antibiotic therapies associated with colchicine is suggested. Dental procedures in the oral cavity such as the removal of dental caries and the removal of dental plaque may be associated with changes in the microbiome of the saliva and can have positive effect on the progress of BD.

Keywords

Behcet's disease · Microorganisms · Microbiota

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18.1 Introduction

Behcet's disease or syndrome (BD/BS) is a multi-organ disease involving several apparatus such as skin, mucosal membranes, joints, eyes, veins, arteries, the gastrointestinal system, and the central nervous system. Behcet's geographical distribution runs through the ancient silk road: from the Mediterranean, including Turkey (370 cases per 100,000), to East Asia. By contrast, it is rarer in Northern Europe, North America, Australia, and Africa (Tong et al. 2019). Although this peculiar distribution may suggest a genetic etiology, it is known that the etiopathogenesis of BD is characterized by a complex interaction between lifestyle, age, sex, mechanical trauma, immune system, and microbiome in individuals with a specific genetic predisposition (Mumcu and Direskeneli 2019). In particular, the properties of the oral and intestinal microbiome seem to be important contributing causes of BDs etiopathogenesis.

18.2 The Microbiome and Immunity

The human body is densely populated by commensal germs mainly occupying the gastrointestinal system, the skin, the uro-genital tract, and the oral cavity. The term microbiota refers to the whole genome of these microorganisms (prokaryotes, viruses, and eukaryotes) and their ecosystem. The types and abundance of each of them have an important inter- and intra-individual difference and depend on factors such as the environment, diet, and genetic characteristics of the host. The microbial ecosystem greatly affects the health of the host. In fact, the genes encoded by our microbial colonizers are 100 times more than those encoded by the human genome (The Human Microbiome Project Consortium 2012; Tong et al. 2020). The microbiome shapes the development of the immune system since infancy, this coexistence is necessary to allow immune tolerance towards commensal microbial components, especially the intestinal ones. In fact, it is thought that the microbiome may be an important player in autoimmunity, and that the loss of the immune tolerance mechanism may be caused by changes in microbiome's microbial composition (Goris and Liston 2012; Konig 2020; Li et al. 2018). The relevance of the microbiota in shaping the host immunity is best observed in germ-free (GF) models. Studies on GF mice highlight an "underdeveloped" innate and adaptive immune system (reduced expression of antimicrobial peptides, reduced IgA production, fewer types of T cells), underlining the crucial role of these microorganisms to induce complete maturation of the immune system. Other studies comparing GF mice to mice colonized with three strains of bacteria (*E. coli* K-12, *Staphylococcus xylosus*, and *Enterococcus faecalis*) reported that GF mice have a delayed microbial clearance, a reduced inflammatory response to *E. coli* K12, and a reduction in the myeloid cell pool (Balmer et al. 2014; Tomkovich and Jobin 2016). The alterations of this complex quantitative and qualitative balance of microbiota's microorganisms are defined as dysbiosis, and as reported by numerous studies, they can be a contributing cause of different immune diseases including BD, ankylosing

spondylitis, rheumatoid arthritis, systemic lupus erythematous (SLE), diabetes mellitus, and multiple sclerosis. The classic way the microbiota influences immune homeostasis involves pattern recognition receptors (PRR) located on macrophages, such as toll-like receptors (TLR) (Akira et al. 2006; Tong et al. 2020), dendritic cells (DCs), and epithelial cells, which in the innate immune systems play a role in detecting microbial components or products. One example of immunomodulatory bacteria is *Bacteroides fragilis*. Its polysaccharide A (PSA) is recognized by TLR2 and is able to influence the development and homeostasis of T lymphocytes and to induce interleukin-10 (IL-10) production by $CD4^+$ T lymphocytes. *Lactobacillus Plantarum*, whose signal is similarly carried by TLR2, promotes the pro-inflammatory cytokines' production by dendritic cells modulating regulatory T lymphocytes (Tomkovich and Jobin 2016). Invasive *E. coli* induces the production of cytokines in vitro, especially IL-1, by activating the nucleotide-binding oligomerization domain 3 (NLRP3) inflammasome in macrophages. *Staphylococcus epidermidis*, interacting with $CD103^+$ DCs, induces the expression of $CD8^+$ T lymphocytes in the epidermis and increases its barrier function. *Lactobacillus rhamnosus* GG (LGG) promotes the bone mass increase in mice by increasing the production of butyrate (Tong et al. 2020; Tyagi et al. 2018).

Butyrate is a metabolite involved in protection of the integrity of the intestinal epithelial barrier, and maintenance of the host immune homeostasis by inducing the differentiation of regulatory T cells (Tregs) (Furusawa et al. 2013; Wang et al. 2012; Ye et al. 2018). It is therefore evident that the role of the microbiota in the modulation of our immune system is not only related to the direct mechanism of the various microorganisms, but also to the indirect one, through the metabolites produced by the microorganisms themselves. Specifically, some intestinal microbes defined as BPB (butyrate-producing bacteria) can produce short-chain fatty acids (SCFAs), with propionate, acetate, and butyrate as the most common (Tomkovich and Jobin 2016). Butyrate increases the amount of regulatory T cells in both the intestines and bone marrow, stimulating $CD8^+$ T cells to secrete the Wnt ligand (Wnt10b), resulting in the activation of osteoblasts and stimulation of bone formation (Tong et al. 2020). Acetate is involved in the intestinal immunoglobulin A (IgA) response via G-protein-coupled receptor 43 (GPR43). GPR43-deficient mice have reduced levels of IgA in their intestines, and the administration of acetate promotes intestinal IgA production, but not in GPR43-deficient mice (Tong et al. 2020; Wu et al. 2017). Acetate stimulates the DCs to promote the IgA class switching of B cells and therefore their production (Tong et al. 2020). Methanogens (which produce methane), another type of gastrointestinal tract's commensal bacteria, suppress the inflammatory response and reduce the oxidative stress in various tissues and organs [retina (Wu et al. 2015), colon (Zhang et al. 2016), liver (Ye et al. 2015), and brain (Shen et al. 2016)]. Finally, another class of pro-inflammatory bacteria called SRB (sulfate-reducing bacteria) inhibits β-oxidation and degrades butyrate (Lv et al. 2016; Ye et al. 2018). Furthermore, hydrogen sulfide (H_2S), which is a cytotoxic byproduct of SRB, has pro-inflammatory effects when at high concentrations (Bhatia 2015; Ye et al. 2018; Zeidan et al. 2016). The host's immune homeostasis, maintained by methanogens and BPBs, can be altered by excessive growth of

Table 18.1 Microbiome and Behcet disease

	BS microbiome	Results
BPB	*Roseburia*, *Subdoligranulum*, *Megamonas*, and *Prevotella*	Exacerbation of disease activity Molecular mimicry (HSP60 kDa and HSP70 kDa proteins, S antigen, IRBP, α-tropomyosin, and αβ-crystalline) Production of pro-inflammatory cytokines (IL-17 and IFN-γ).
SRB	*Bifidobacterium*, *Eggerthella*, and *Bilophila* spp.	
SCFAs	Butirrato	T helper (Th1)/Th17

(Abbreviations: *SCFAs* short-chain fatty acids, *BPB* butyrate-producing bacteria, *SRB* sulfate-reducing bacteria)

some opportunistic pathogens such as *Stenotrophomonas* spp., *Actinomyces* spp., and *Paraprevotella* spp., with a consequent reduction of BPB and methanogens. These anomalies can induce damage to the intestinal epithelial barrier, facilitating the entry into the IEC (intestinal epithelial cells) of the effector molecules associated with microbes and pathogen-associated molecular patterns (MAMP/PAMP) and a consequent overexpression of the corresponding pattern recognition receptors (PRRs) (e.g., TLR2/TLR4) (Ye et al. 2018) (Table 18.1).

18.3 Behcet's Syndrome and the Microbiome

Nowadays, it is now known that the properties of the oral and intestinal microbiome contribute to several factors of BDs multifactorial etiopathogenesis (Fig. 18.1). Their effects on mucosal immunity, inflammation, and disease progress may provide clues for new treatment techniques.

18.3.1 The Intestinal Microbiome in BD

As far as the intestinal microbiome is concerned, numerous studies conducted on fecal samples have observed a reduced bacterial diversity in BD. A reduced presence of the genera *Roseburia*, *Subdoligranulum, Megamonas*, and *Prevotella* belonging to the class of BPB and of the genus *Clostridium* spp. and Methanogens (*Methanoculleus* spp. and *Methanomethylophilus* spp.) was observed. By contrast, a higher prevalence of the genera *Bifidobacterium, Eggerthella,* and *Bilophila* belonging to the SRB class was observed, as well as of various opportunistic pathogens (*Parabacteroides* spp. and *Paraprevotella* spp.) (Mumcu and Direskeneli 2019). The above changes in the bacterial composition of patients with BD represent a clear example of intestinal dysbiosis. A comparison was made between BD patients stratified by ocular (uveitis), mucocutaneous, and vascular involvement. *Prevotella* and *Faecalibacterium* were the most abundant genera in all three groups,

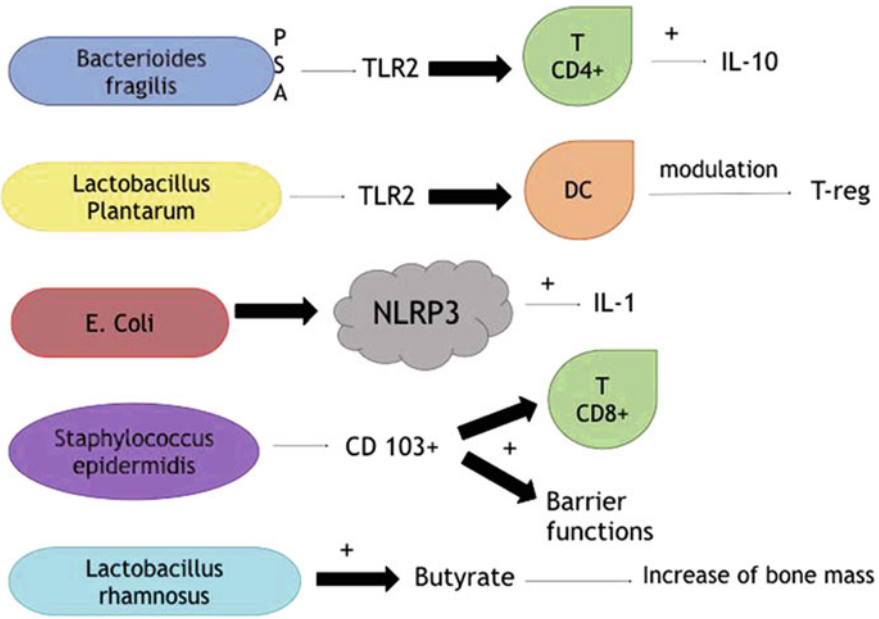

Fig. 18.1 Microorganisms and mechanisms of Behcet disease

but comparing the three different organ systems involved, the linear discriminant analysis effect size (LEfSe) analysis revealed a difference in the following genera *Lachnospiraceae* NK4A136 was found in the uveitis group, *Dialister*, *Intestinimonas,* and *Marvinbryantia* in the mucocutaneous group, and *Gemella* in the vascular group. A 2.5% of *Treponema* was also found in the uveitis group and not in the other two (Bilge et al. 2020).

With respect to the gastrointestinal involvement, a prevalence of the genus *Collinsella* and *Enterorhabdus* spp. belonging to the phylum of *Actinobacteria* has been highlighted. The abundance of *Collinsella* is positively associated with circulating insulin levels and negatively associated with the consumption of dietary fibers. Low dietary fiber content will facilitate *Collinsella* overgrowth and impair the overall fermentation (Bilge et al. 2020; Gomez-Arango et al. 2018). *Collinsella* spp. have also been isolated in patients with Crohn's disease (Biedermann et al. 2013; Bilge et al. 2020; Hov et al. 2015) and *Enterorhabdus* spp. in animal models of colitis (Hov et al. 2015). This is consistent with the alterations observed in the cohort of BD patients examined, in which there was a greater gastrointestinal involvement (Bilge et al. 2020). Finally, Oezguen et al. (2019) carried out a study enrolling only patients with neuro-Behcet disease (NBD), concluding that there is a prevalence of *Prevotella* and *Bacteroides* (Tecer et al. 2020).

18.3.2 The Salivary Microbiome in BD

The salivary microbiome is an easily accessible source of biomarkers. A dysbiosis here can easily allow us to differentiate BD patients from healthy individuals (Coit et al. 2016). In a healthy oral cavity, there are eight main bacterial phyla (*Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, *TM7*, *Spirochaetes*, and *Synergistes*) (Bik et al. 2010). *Streptococcus* is known to be the most abundant, followed by *Haemophilus*, *Neisseria*, *Prevotella*, *Veillonella*, and *Rothia*. Members of the phylum *Actinobacteria*, particularly the genus *Rothia* (Seoudi et al. 2015), *Streptococcus salivarius* and *Streptococcus sanguinis* are on the other hand, those most represented in the oral mucosa of patients with BD. Ulcer sites are more frequently colonized by the genus *Streptococcus* rather than by the genus *Rothia*. In another study, it was found that the *Prevotella* genus was more frequently detectable in the saliva of BD patients presenting with oral ulcerations (Marchini et al. 2007; Seoudi et al. 2015). However, the use of immunosuppressants resulted in an increased presence of *Bergeyella, Prevotella,* and *Porphyromonas catoniae* (Coit et al. 2016; Mumcu and Direskeneli 2019).

18.3.3 The Role of Dysbiosis

One of the mechanisms by which dysbiosis can probably lead to the triggering of a pro-inflammatory process is molecular mimicry. This mimicry is due to sequence homology in heat shock protein (HSP) between the microbial and human peptides triggering autoimmune processes in BD patients. Several autoantigens have been observed: HSP60 kDa and HSP70 kDa proteins, S antigen, interphotoreceptor retinoid-binding protein (IRBP), α-tropomyosin, and αβ-crystalline (Tecer et al. 2020). Moreover, in order to state whether or not the gut microbiome has a role in the development of BD, a fecal transplant has been done in mice with autoimmune uveitis. The mice that have been colonized by gut microbiome of BD patients presented an exacerbation of disease activity and an increase in production of pro-inflammatory cytokines in excess (Ye et al. 2018), especially IL-17 and IFN-γ (Mumcu and Direskeneli 2019; Ye et al. 2018). Most of the studies have focused particularly on the community of bacterial of the microbiome, but Ye et al. found that *Atkinsonella texensis*, *Trichoderma parareesei*, *Colletotrichumorbiculare*, *Exophiala mesophila*, *Candida parapsilosis*, *Claviceps paspali*, *Drechslerella stenobrocha*, and *Shiraia* spp. are dominant fungal species in the fecal microbiome of BD patients which would deserve further investigation (Tecer et al. 2020).

18.3.4 The Role of the SCFAs

As discussed in the previous paragraph, the presence or absence of certain microorganisms is not the only factor participating in the pathophysiology of inflammatory diseases, in this case of BD, but also the metabolites produced by

the aforementioned bacteria play an important role. The amount of SRB is negatively associated with that of BPB and methanogens in the BD group. When SRB and BPB were co-cultured with lactate-producing bacteria, high levels of H2S and low levels of butyrate were found (Ye et al. 2018). In fact, it has been shown that the dysbiosis present in these patients has led to key changes in the profiles of SCFA production (Consolandi et al. 2015). A significant decrease in butyrate producers (such as *Roseburia* and *Subdoligranulum*) has been demonstrated. Butyrate induces the differentiation of Treg cells, and its reduction may promote a potent immunopathological T cell response (Kosiewicz et al. 2014; Pagliai et al. 2020a), as demonstrated by the higher ratio of T helper (Th1)/Th17 cells in the intestinal mucosa of BD patients (Emmi et al. 2016; Pagliai et al. 2020a). Drugs used to treat BD are likely to have various effects on gut microbes. Shimizu et al. (2019) performed a metagenomic analysis in patients with BD, where 13 adult patients with BD were enrolled: 31% with uveitis, 15% with central nervous system involvement, 85% in treatment with colchicine, 38% on steroid therapy, 15% on cyclosporine therapy, and none on biologics.

This study underlined an important increase in the levels of *Eggerthella lenta*, *Lactobacillus mucosae*, *L. iners*, *L. salivasirus*, *Acidaminococcus* spp., *Bifidobacterium bifidum*, and *Streptococcus* spp. (Shimizu et al. 2019). However, other studies have shown that colchicine (daily doses of 0.79 ± 0.26 mg) had little effect on the intestinal microbes and intestinal mucosa of the host (Iacobuzio-Donahue et al. 2001; Shimizu et al. 2016; Ktsoyan et al. 2013). Cyclosporine (125 and 50 mg daily doses) and azathioprine (75 mg daily dose) may also have marginal effects on gut microbes (Shimizu et al. 2016).

18.3.5 The Role of Smoking

Cigarettes produce up to 4000 chemical compounds including hydrogen, hydrogen cyanide, methane, phenols, nicotine, hydrocarbons, and heavy metals (Agbetile et al. 2012). These compounds influence both the intestinal and oral microbiome (Capurso and Lahner 2017). In addition a wide bacterial diversity in cigarettes, ranging from soil and commensal microorganisms to potential human pathogens, including *Acinetobacter*, *Bacillus*, *Burkholderia*, *Clostridium*, *Klebsiella*, and *Pseudomonas aeruginosa*, has been revealed (Biedermann et al. 2013). Most studies on the gut microbiome evaluate the effects of smoking on animal models (Capurso and Lahner 2017; Verschuere et al. 2012). An anti-inflammatory effect of nicotine resulting in the abolition of pro-inflammatory cytokines synthesis, including IL-1β and TNF-α, has been reported (Capurso and Lahner 2017). A reduction of *Prevotella* and *Neisseria* spp. and an increase of *Firmicutes*, mainly *Streptococcus* spp. and *Veillonella* spp., together with the genus *Rothia* (*Actinobacteria*) in the upper gastrointestinal tract (GIT) of smokers have been demonstrated (Huang and Shi 2019). As a result, smoking withdrawal leads to further changes in the microbiome, with an increase in microbial diversity (Biedermann et al. 2013), in particular increase in *Firmicutes* and *Actinobacteria* and a decrease in *Bacteroidetes* and *Proteobacteria* (Capurso and Lahner 2017).

Toxic components and bacteria in cigarettes also have an impact on the oral microbiome through numerous mechanisms: immunosuppression, oxygen deprivation, and biofilm formation (Huang and Shi 2019; Macgregor 1989), leading to the loss of beneficial oral species and colonization by pathogens (Huang and Shi 2019; Nociti et al. 2015). The results of bacterial cultures taken on smokers have highlighted a reduction of *Neisseria* or *Branhamella* (Colman et al. 1976; Ertel et al. 1991; Huang and Shi 2019). Microbial profiles of subgingival plaque samples of smokers have a highly diversified anaerobic microbiome, rich in pathogens and poor in commensal microorganisms, more closely related to pathological pictures (Huang and Shi 2019). It is known that tobacco smoke affects the immune system through a reduction in the activity of natural killer cells, an increase in white blood cells (Capurso and Lahner 2017; Maldonado-Contreras et al. 2011) and phagocytes, with decreased function and increased expression of surface receptors (e.g., TLR2) (Capurso and Lahner 2017; Engstrand and Lindberg 2013; Stearns et al. 2011). Therefore, smoke-related immunosuppression may allow colonization of new bacteria. Despite having a negative effect on autoimmunity (Mumcu and Direskeneli 2019; Perricone et al. 2016), several studies have noticed the protective effect of smoking on the development of oral ulcers in BS (Soy et al. 2000; Tuzun et al. 2000). The beneficial effects of smoking on recurrent oral ulcers are related to the increased epithelial proliferation of oral mucosa and the systemic anti-inflammatory effects of nicotine (Kalayciyan et al. 2007). In smokers, an increased tolerance to microbial factors due to local effects related to the tobacco habit has been highlighted (Iris et al. 2018). Smoking cessation may even be considered a trigger for oral ulcers (Soy et al. 2000).

18.4 Therapy

18.4.1 Diet

Several studies suggest that diets rich in plant-based foods have a beneficial role on health by modulating the microbiome and consequently the metabolites production (De Filippis et al. 2016; Kabeerdoss et al. 2012; Pagliai et al. 2020a, b). In fact, diets rich in unrefined grains, fruits, vegetables, and legumes have been reported to promote a healthier gut microbiota (GM) profile. These fermentable substrates act as sources of metabolic fuel for GM fermentation, which in turn results in end products, mainly SCFA, which are key microbial metabolites with a multifactorial role in host health (Holscher 2017; Pagliai et al. 2020a). Foods rich in inulin, such as chicory, artichokes, and onions, and foods rich in resistant starch, such as cooked and chilled rice, pasta, or potatoes, have been associated with increased butyrate production (Candela et al. 2010; Pagliai et al. 2020a). In this regard, a recent study compared microbial and metabolic changes after a 3-month dietary intervention, reporting a positive association between carbohydrate consumption and fecal butyrate levels and a negative association between intake of fats and propionate and acetate. Negative associations between SCFA and levels of several inflammatory cytokines were also observed.

18.4.2 Antibiotics

In addition to the diet, other studies were carried out on the use of antibiotic therapies associated with colchicine. Specifically, prophylactic benzathine penicillin combined with colchicine appears to be more effective in controlling the mucocutaneous manifestations of BD (including oral ulcers) than colchicine alone (Calgüneri et al. 1996; Mumcu and Direskeneli 2019). Minocycline reduces the frequency of mucocutaneous symptoms in BD (Kaneko et al. 1997). Azithromycin administered for 4 weeks to eight patients with severe mucocutaneous symptoms suppresses the number of follicolytis lesions and reduces the healing time of oral ulcers (Mumcu et al. 2005). In another study, pre-treatment intracellular IFN-γ responses of peripheral blood mononuclear cells to *Streptococcus sanguinis* and lipoteichoic acid are higher than in post-treatment samples, also suggesting an immunomodulatory effect of azithromycin (Mumcu et al. 2013; Mumcu and Direskeneli 2019).

18.4.3 Oral Health and Dental Interventions

Finally, it seems appropriate to assess whether interventions in the oral cavity with the removal of dental caries and/or the removal of dental plaque may be associated with changes in the salivary microbiome and whether these can be positively correlated with the progress of BD. A study was carried out finding no changes in the bacterial community before and after treatment. These data are in line with a previous study which showed that periodontal therapy in healthy individuals with periodontal disease significantly alters the dental plaque microbiome, but not the salivary microbiome (Coit et al. 2016; Yamanaka et al. 2012). Another study, by Karacayli et al. (2009), on 58 patients, in addition to the standard medical treatment, added oral hygiene education to the control group, while dental and periodontal treatments were also performed in the intervention group. Although at the first check-up, after 2 days, an increase in the number of new ulcers is observed in the intervention group, after 6 months this is significantly lower. These data suggest that dental and periodontal treatments may help to decrease oral symptoms in BD patients. Therefore, regular dental check-ups, prophylaxis, and treatments should be recommended in the management of the disease in patients with BD (Karacayli et al. 2009; Mumcu et al. 2004; Mumcu and Direskeneli 2019).

18.5 Conclusion

The mutual balance in which the commensal and pathogenic microorganisms resident in the skin or mucosa are maintained is protected by the integrity of the skin/mucosal barrier and the active surveillance of the innate and adaptive immune systems. BD is characterized by important alterations both anatomical and physiological aspects of the mucosa and therefore provides a predisposing environment for the onset of dysbiosis. Once it has occurred, dysbiosis leads to the release of

microbial peptides and other molecules that amplify a state of chronic inflammation as a result of the activation of effector cells belonging to both immune systems. One of the mechanisms by which dysbiosis can probably lead to the triggering of a pro-inflammatory process is molecular mimicry. Several studies have evaluated the role of dysbiosis in the BD pathogenesis and activity. Counteracting dysbiosis by means of prebiotics or probiotics may represent a useful tool in preventing or limiting inflammation in BD. Unfortunately, no RCTs on the effectiveness of such strategies are available, and currently published studies are not conclusive due to heterogenicity in methodology. It is likely that a normocaloric diet with a high fiber and vitamins contain together with a weight control could be useful for patients in reducing the inflammatory burden and could be considered beside the pharmacologic intervention.

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Microorganisms in the Pathogenesis and Management of Immune Thrombocytopenia (ITP)

19

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Abstract

Immune thrombocytopenia (ITP) represents an immune-mediated condition characterized by isolated thrombocytopenia due to the production of autoantibodies directed at human thrombocytes with a subsequent decrease in the platelet count below 100,000 platelets/mmc. Microbial pathogens have emerged as key players in the development of ITP and are frequently listed as causes in the development of secondary ITP in adults, alongside autoimmune disorders, immune deficits, blood cancers, and others. This chapter briefly reviews the role of *Helicobacter pylori*, HIV, HCV, HBV, and SARS-CoV-2 (the viral agent responsible for the development of COVID-19) in the pathogenesis and management of ITP. In addition, the role of the gut microbiota and post-vaccination ITP is discussed.

Keywords

Immune thrombocytopenia · *Helicobacter pylori* · Gut microbiota · Microbiome · HIV · HCV · HBV · COVID-19 · Vaccination

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19.1 Introduction

Immune thrombocytopenia (ITP) represents an immune-mediated condition characterized by isolated thrombocytopenia due to the production of autoantibodies directed at human thrombocytes with a subsequent decrease in the platelet count below 100,000 platelets/mmc. ITP can be either primary (approximately 80% of cases, either acute or chronic) or secondary (20% of cases, caused by autoimmune or chronic lymphoproliferative disorders, infections, and others). The immune-mediated destruction of thrombocytes occurs via the binding of anti-platelet antibodies to the GPIIb/IIIa complex on the surface of thrombocytes which are consequently entrapped by spleen macrophages and subjected to phagocytosis. In addition, the intramedullary destruction of megakaryocytes can occur when autoantibodies bind to precursor cells. Oxidative stress can also play a role in infection-related secondary ITP when the destruction of thrombocytes occurs via overproduction of reactive oxygen species. Acute ITP represents 80–90% of ITP cases in children and has a sudden onset, often following viral infections, variable hemorrhagic manifestations (<1% may develop intracerebral hemorrhage), and may resolve spontaneously in the majority of cases. Chronic ITP most often affects young females, has an insidious onset and a long-lasting evolution. Hemorrhagic manifestations mostly comprise mucocutaneous bleeding, whereas intracerebral hemorrhage may develop if the thrombocytopenia is severe. ITP diagnosis is one of the exclusions and is based on anamnesis, clinical examination of the patient, laboratory data (reduced platelet count; peripheral blood smear showing thrombocytopenia often with large/giant platelets as a sign of accelerate thrombocyte production due to exaggerated destruction), longer bleeding time with a normal Quick Time (prothrombin time), aPTT and fibrinogen levels. Primary ITP must be differentiated from pseudothrombocytopenia, drug-induced thrombocytopenia, or thrombocytopenia that develops during the course of autoimmune or lymphoproliferative disorders, myelodysplastic syndromes, pregnancy, congenital causes, consumption coagulopathy, and others. The treatment of ITP comprises 1st (steroids, intravenous immunoglobulins) or 2nd line agents (open total or laparoscopic splenectomy; thrombopoietin receptors agonists, i.e., romiplostim and eltrombopag; rituximab). Immunosuppressive agents (cyclosporine, cyclophosphamide, vinka alkaloids, azathioprine etc.) can sometimes also be employed in selected cases (Diz-Küçükkaya and López 2016; Gaman and Gaman 2017a, 2014; Liebman and Pullarkat 2011; Grace and Neunert 2016; Cunningham 2020; Neunert et al. 2019).

Microbial pathogens have emerged as key players in the development of ITP and are frequently listed as causes in the development of secondary ITP in adults, alongside autoimmune disorders, immune deficits, blood cancers, and others. During the pediatric age, ITP usually develops post-vaccination or post-viral infections (Diz-Küçükkaya and López 2016; Gaman and Gaman 2017a; Li et al. 2020; Schifferli et al. 2021).

The interest towards the crosstalk of microbial pathogens and ITP has steadily increased in parallel with a better understanding of the pathogenesis and improvements in the management of this disorder. An up-to-date search in the

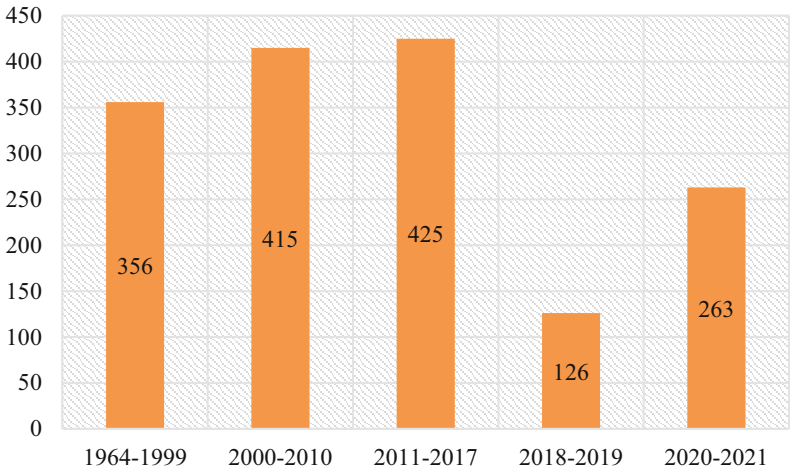

Fig. 19.1 Number of articles indexed in PubMed/MEDLINE between 1964 and 2021 and exploring the relationship of microbial pathogens and ITP

PubMed/MEDLINE database since its inception until September 18th 2020 revealed that over 1500 publications have explored this topic, with more than 15% of the manuscripts being published between 2020 and 2021, most likely in direct relationship with the onset of the coronavirus disease 2019 (COVID-19) pandemic. Figure 19.1 displays the number of papers investigating the links between ITP and microbial pathogens as detected in the aforementioned database (PubMed/MEDLINE 2021). The objective of this chapter is to review the associations between microbial pathogens, i.e., bacteria, viruses, and fungi, and ITP and to discuss role of probiotics in management of ITP.

19.2 Bacteria and ITP

19.2.1 *Helicobacter pylori* and ITP

Secondary ITP can develop as an extragastric manifestation of the infection with *Helicobacter pylori* with the accurate antibiotic targeting of this pathogen leading to the resolution of ITP and often to a normal thrombocyte count. The link between the onset of secondary ITP and the infection with this germ has mostly been established in studies derived from low/middle-income countries, where the prevalence of the aforementioned infection remains high, whereas in high-income areas the association was not as robust. For example, O'Neill et al. (2019) pointed out that among the population of the USA, the infection was more frequently encountered in Hispanic individuals versus Caucasians (52.7% versus 13%, $P = 0.007$). However, the results of a recently published international survey study revealed that screening for *Helicobacter pylori* infection was higher in hematology practitioners in Asia and

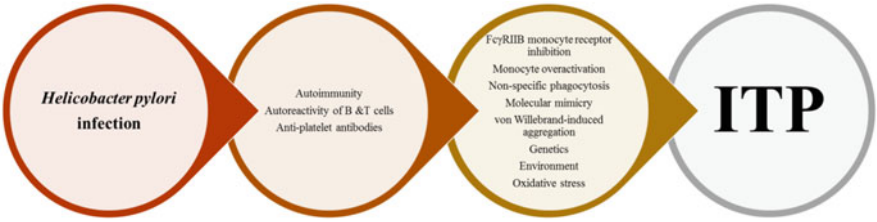

Fig. 19.2 The link between *Helicobacter pylori* infection and ITP

the Middle-East versus other parts of the world, suggesting that ITP secondary to this infectious agent might be sometimes overlooked (Vishnu et al. 2021). Several of the pathophysiological events (Fig. 19.2) associated with autoimmunity, autoreactivity of B and T cells, and the development of anti-platelet antibodies in *Helicobacter pylori* infection include: inhibition of the FcγRIIB monocyte receptor with subsequent overactivation of the function of these cells and non-specific phagocytosis, molecular mimicry between the *Helicobacter pylori* components (sequences of amino acids present in the VacA and CagA antigens and urease B) and thrombocyte surface glycoproteins (e.g., GPIIIa), von Willebrand-induced aggregation of thrombocytes, genetic factors (the subjects harboring class II HLA-DRB1*11, HLA-DRB1*14, and HLA-DQB1*03 alleles are more prone to be infected with *Helicobacter pylori*), von Willebrand factor-induced aggregation of thrombocytes, oxidative stress, interleukin-1β gene polymorphisms, environmental factors, and others (Campuzano-Maya 2014; Franchini et al. 2017; Gaman and Gaman 2017b; Kuwana 2014). In the vast majority of patients, eradication of the pathogen following a 7–14 course of triple therapy regimens based on one proton-pump inhibitor and two antibiotics (generally amoxicillin and clarithromycin) normalizes the platelet count (Vanegas and Vishnu 2019).

19.2.2 Gut Microbiota and ITP

Liu et al. (2020) demonstrated the presence of dysbiosis in individuals newly diagnosed with primary ITP. As compared to controls with a normal status of health, there were fewer phyla detected in ITP, i.e., eight versus ten. The most predominant phyla in ITP was *Bacteroidetes*, whereas in controls *Firmicutes* predominated. Individuals living with ITP displayed a higher percentage of *Bacteroidetes* (45.96% versus 34.26%) and *Actinobacteria* (1.22% versus 0.90%) and an elevated *Bacteroidetes*/*Firmicutes* ratio, whereas *Firmicutes* and *Proteobacteria* were less represented (38.59% versus 50.92% and 11.43% versus 13.60%, respectively). *Fusobacteria* represented 1.29% of the ITP phyla. In terms of diversity, there was a statistically significant elevation in *Anaerorhabdus sutterella* in ITP and in healthy individuals of *Carnobacteriaceae*, *Clostridium_XI*, and *Peptostreptococcaceae* (Liu et al. 2020). The limitations of their study were pointed out by Zhao and Chen (2020) who argued that the dietary pattern, the age of the subjects (changes in the

representation of *Firmicutes* and *Bifidobacterium* are age-dependent), and whether the patients underwent antibiotic therapy for the infection with *Helicobacter pylori* influence the composition of the intestinal microbiome (Zhao and Chen 2020).

Zhang et al. (2020) also assessed the composition of the gut microbiome in primary ITP subjects and reported that the majority of the phyla pertained to *Firmicutes, Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*. Individuals diagnosed with primary ITP displayed elevated percentages of *Lactobacillales* (which belong to the *Firmicutes*), *Streptococcus* (*Streptococcus anginosus*, *Streptococcus parasanguinis*, and *Streptococcus salivarius*), *Enterococcus*, *Leuconostocaceae* (in particular *Weissella*), and *Actinomycetaceae*. However, the authors recorded a depletion in *Bacteroidetes* (in particular *Bacteroides* and *Bacteroides vulgatus*), *Lachnospiraceae UCG-010* and *Lachnospiraceae UCG-010 sp.* in primary ITP. Consequently, a reduced *Firmicutes*/*Bacteroidetes* ratio, perceived as a signal for dysbiosis, was found in individuals with primary ITP versus healthy volunteers. In terms of laboratory data, the thrombocyte count was negatively associated with *Lactobacillales* (*Streptococcus* sp. such as *S. anginosus* and *S. salivarius*) and positively associated with *Bacteroidetes* (Zhang et al. 2020).

Gut microbiota has also been linked to treatment options in primary ITP. In primary ITP patients who were not prescribed any drug displayed *Ruminococcus gnavus*, *Bifidobacterium longum* and *Akkermansia muciniphila* were highly prevalent. In primary ITP, the well-represented genera pertained to *Actinobacteria* (*Bifidobacterium*, *Gardnerella*, and *Frankia*), *Fusobacteria* (*Fusobacterium*), *Verrucomicrobia* (*Akkermansia*), *Firmicutes* (*Desulfosporosinus*, *Intestinibacter*, *Lactococcus*, *Mitsuokella*, and *Thermicanus*), and *Proteobacteria* (*Enterobacter*, *Kluyvera*, *Raoultella*, and *Moraxella*). Healthy volunteers were abundant in genera pertaining to *Firmicutes* (*Paeniclostridium*, *Dielma*, *Paraclostridium*, and *Carboxydothermus*) and *Proteobacteria* (*Shewanella*, *Syntrophobacter*, and *Janthinobacterium*). In terms of species, the intestinal microbiome of primary ITP patients displayed abundance in *Prevotella* sp., *Enterobacter* sp., *Bifidobacterium* sp., *Fusobacterium* sp., and *Bacteroides* sp.; however, depletion in two *Bacteroides* sp. and *Flavobacterium* sp. was also detected in the aforementioned group. On the one hand, the gut microbiota of treatment-naïve subjects was more diverse as compared to the subjects with a normal status of health, and the researchers were able to identify several metagenomic species particular to the subgroup of patients who were not prescribed any therapy, i.e., microbes with an annotation mostly to *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*. On the other hand, the prescription of certain drugs, namely corticosteroids and danazol, was shown to lead to alterations of the intestinal microbiota in ITP. Interestingly, in the individuals who were diagnosed with resistance to corticosteroids, the *Pedobacter* genera and the *Clostridium tyrobutyricum*, *Bifidobacterium scardovii*, butyrate-producing bacterium SM4/1, and *Prevotella* sp. oral taxon 472 species were highly prevalent, whereas the *Rhodonellum* and *Lachnobacterium* genera and several species pertaining to *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* displayed a reduced prevalence. Moreover, the only common depletion in both treatment-naïve and

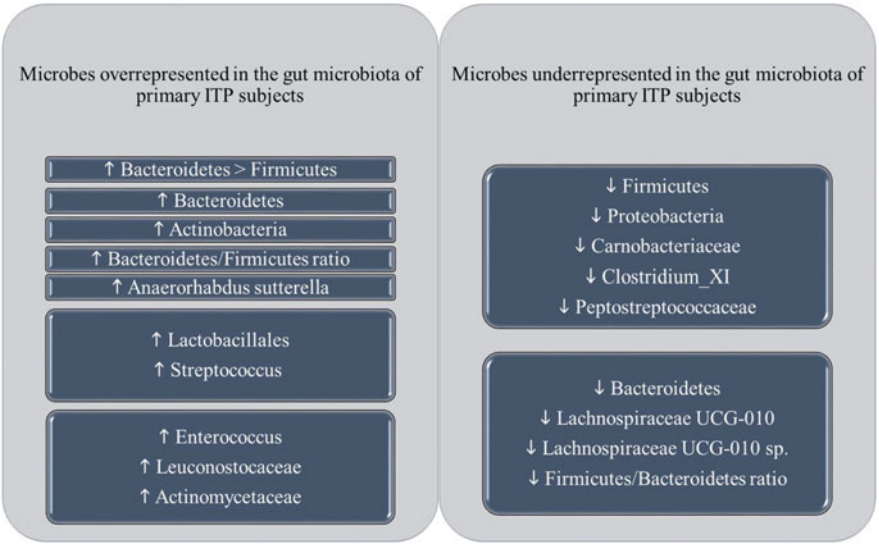

Fig. 19.3 Over- and underrepresented microbes in the gut microbiota of primary ITP

corticosteroid-resistant subjects with primary ITP affected the *Lachnoanaerobaculum_sp._MSX33 species* (Wang et al. 2021).

Malnick et al. (2015) reported the development of ITP in a patient infected with *Clostridium difficile* who underwent two fecal microbial transplantations from the same HIV, HCV, and *Helicobacter pylori* triple-negative donor. At 4–5 days after each procedure, the subject's thrombocyte count decreased to 17,000 platelets/mmc and 20,000 platelets/mmc, respectively, and IgM, IgG, and IgA antibodies directed against the subject's thrombocytes were detected. Based on their experience, the authors recommended that the platelet count should be monitored for at least 2 weeks following fecal microbial transplantation to screen for ITP (Malnick et al. 2015). Figure 19.3 depicts the over/underrepresented microbes in the gut microbiota of primary ITP.

19.3 Viruses and ITP

19.3.1 HIV and ITP

Abdullah et al. (2021) examined 374 bone marrow samples collected from individuals with confirmed HIV infection and reported that the presence of isolated thrombocytopenia in HIV-positive subjects was due to the development of ITP (Abdullah et al. 2021). ITP develops via several mechanisms, namely peripheral destruction of thrombocytes (in the early stages of the disease), reduced generation of thrombocytes and deregulated production of hematopoietic cells (in the late stages

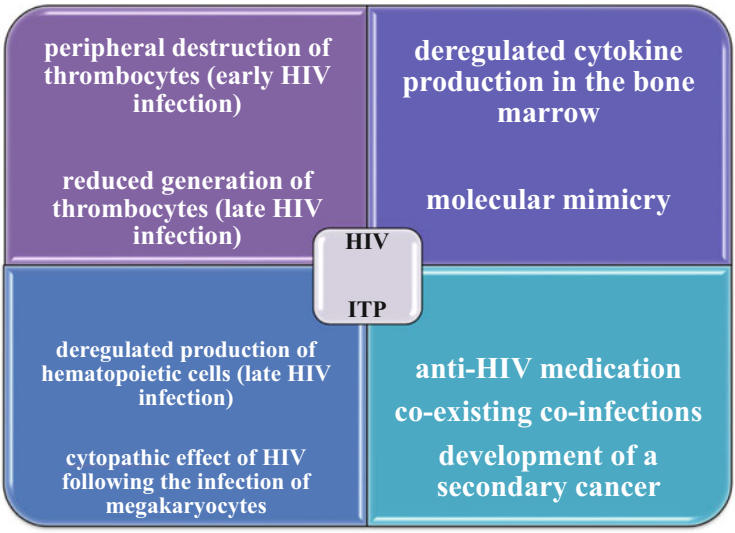

Fig. 19.4 Mechanisms driving HIV-induced ITP

of the infection), molecular mimicry (between platelet surface receptors and HIV proteins), infection of megakaryocytes by HIV with subsequent cytopathic actions of the virus, deregulation of the production of cytokines in the bone marrow, as well as ITP induced by anti-HIV medication and/or co-existing co-infections (e.g., HCV, opportunistic infections) or related to the development of a secondary cancer (Franchini et al. 2017; Cines et al. 2009). The management of HIV-related ITP depends on the stage of the HIV infection, with Cines et al. (2009) revealing that individuals in the late stages of HIV infection will respond better to anti-HIV treatment rather than individuals in the early stages of the infection who respond well to standard ITP therapeutic options (steroids, intravenous immunoglobulins, splenectomy, etc.) (Cines et al. 2009). Figure 19.4 depicts the mechanisms driving HIV-induced ITP.

19.3.2 HCV and ITP

Hung et al. (2018) reported that HCV infection is the second most common cause of secondary ITP (approximately 17% of cases) which was only surpassed in frequency by nearly 5% by systemic lupus erythematosus (Hung et al. 2018). Both HCV infection and its co-infection with HBV are linked with an elevated risk of secondary ITP development (odds ratio $\approx$ 54.5 and odds ratio $\approx$ 7, respectively) (Wu et al. 2018). Interestingly, HCV-infected individuals with secondary ITP display elevated concentrations of anti-thrombocyte antibodies when compared to individuals diagnosed with primary ITP (Huang et al. 2020). In terms of pathophysiological explanations of HCV-induced secondary ITP, Huang et al. (2017) demonstrated that

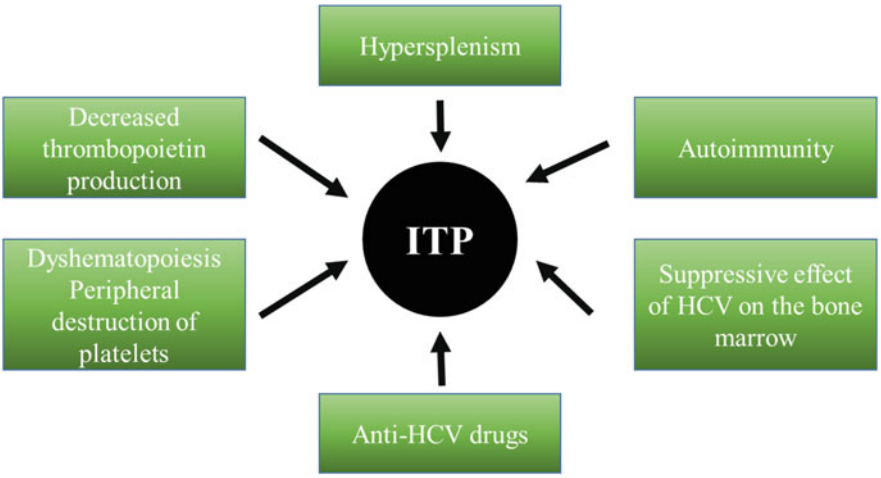

Fig. 19.5 Mechanisms driving HCV-induced secondary ITP

in this affection there is a deregulation of the production of cytokines involved in the production of platelets. The researchers detected an elevation in thrombopoietin (possibly via a positive feedback loop), TNF-α, and interleukin-6 concentrations, whereas interleukin-11 concentrations were low. In addition, a positive association was noted between the thrombocyte count and interleukin-11 concentrations, whereas the association of the thrombocyte count with TNF-α levels was negative (Huang et al. 2017). To name a few, key factors underpinning the onset of secondary ITP in HCV infection are hypersplenism, anti-HCV drugs (e.g., pegylated interferon), defective production of thrombopoietin, autoimmunity (anti-thrombocyte antibodies and thrombocyte-linked immune complexes), suppressive action of HCV on the bone marrow with consequent ineffective hematopoiesis, and peripheral destruction of thrombocytes (Franchini et al. 2017). Figure 19.5 depicts the mechanisms driving HCV-induced secondary ITP.

19.3.3 HBV and ITP

Hung et al. (2018) ranked HBV infection as the third cause (≈13.5% of cases) of secondary ITP in their study group, surpassed only by lupus and HCV infection (Hung et al. 2018). Overall, the risk of developing secondary ITP is rather high when an infection with HBV is present, with Wu et al. (2018) calculating an odds ratio of 18.7 and as aforementioned, the odds ratio is about 7 when co-infection with HCV is detected (Wu et al. 2018). The frequency of ITP is elevated in individuals who test positive for the HBsAg, irrespective of the presence of liver cirrhosis, as well as in subjects with increased bilirubin levels (Joo et al. 2017; Huang et al. 2021). The pathophysiological mechanisms driving the onset of ITP in HBV infection are similar to those described above for the other hepatotropic virus, namely HCV. Of

note, the platelet count has been included in a number of serological scores for the assessment of liver fibrosis, e.g., APRI, FIB-4 index, NAFLD fibrosis score, FibroIndex, FornsIndex, Fibrometer, Lok index, Bonacini-index, King's score, Pohl index, VITRO score, and others (Gheorghe et al. 2021).

19.3.4 SARS-CoV-2 and ITP

On the one hand, there are isolated case reports in the literature that report the onset of ITP following COVID-19. Stepman et al. (2021) reported the case of an 82-year-old-male who presented to the hospital 4 weeks after COVID-19 diagnosis for syncope-like manifestations, epistaxis, and ecchymoses who further developed melena during hospitalization. Therapeutic choices in this case included thrombocyte infusions, steroids, and intravenous immunoglobulins (Stepman et al. 2021).

On the other hand, the COVID-19 pandemic has complicated the diagnosis and management of all hematological disorders, including primary and/or secondary ITP unrelated to the infection with SARS-CoV-2. Rampotas et al. (2021) conducted a real-world prospective study on the topic of ITP management in the UK and revealed that the median time between the manifestations of SARS-CoV-2 infection and ITP was of 12.5 days. Steroids remained the first treatment choice in ITP patients during the pandemic; however, elevated efficacy in ITP management was displayed by thrombopoietin receptor agonists (Rampotas et al. 2021). Guirguis et al. (2021) depicted the cases of two male patients who presented with COVID-19 pneumonia and secondary ITP probably due to SARS-CoV-2 infection who were successfully treated with intravenous immunoglobulins ± steroids (Guirguis et al. 2021). Bhattacharjee and Banerjee conducted a systematic review of the cases of ITP linked to COVID-19 and highlighted that ITP developed most frequently in individuals aged >50 years and with moderate/severe SARS-CoV-2 infection. The cases were successfully treated with steroids, intravenous immunoglobulins, and/or thrombopoietin receptor agonists; however, relapses were noted in about 10% of the subjects (Bhattacharjee and Banerjee 2020). SARS-CoV-2-induced ITP is generated via similar mechanisms to other viral infections, i.e., with HCV and HBV, namely dyshematopoiesis and autoimmunity (autoantibodies and immune complexes targeting or involving platelets), and in addition the cytokine storm (which can cause dyshematopoiesis with subsequent reduced production of thrombocytes), lung injury (elevated the consumption of platelet at the injury site), and secondary hemophagocytic lymphohistiocytosis (Xu et al. 2020).

19.4 Vaccination and ITP

The occurrence of ITP following the administration of a vaccine has been reported particularly in children, yet an elevation in the number of cases has also been noted in relationship with the mass vaccination campaigns imposed by the outbreak of the COVID-19 pandemic (Diz-Küçükkaya and López 2016; Choi et al. 2022).

Secondary ITP has been depicted in individuals who received mRNA-based vaccines (either the BNT162b2 COVID-19 vaccine manufactured by Pfizer-BioNTech or the mRNA-1273 vaccine produced by Moderna) as well as vaccines employing viral vectors, i.e., a Chimpanzee adenovirus (ChAdOx1 nCoV-19 COVID-19 vaccine produced by AstraZeneca). However, the follow-up of these subjects is required to assess whether they indeed experienced secondary ITP or if vaccination facilitated the diagnosis of ITP which could have been primary and previously undiagnosed or whether the vaccine could have triggered the development of primary ITP (Choi et al. 2022; Hernández et al. 2021; Lee et al. 2021; Jasaraj et al. 2021).

Previous to the COVID-19 pandemic, on the one hand, there have been isolated case reports of secondary ITP triggered by the administration of measles-mumps-rubella, varicella, diphtheria-tetanus-pertussis-polio, pneumococcal, meningococcal group C, influenza, and human papillomavirus vaccines (Bizjak et al. 2016; Hamiel et al. 2016; Morin and Sadarangani 2019). On the other hand, several case-control studies have pointed out an association between the measles-mumps-rubella, varicella, tetanus-diphtheria-acellular pertussis, and hepatitis A vaccine in children and adolescents but not in adults (Bertuola et al. 2010; O'Leary et al. 2012; Grimaldi-Bensouda et al. 2012).

19.5 Probiotics, Prebiotics, and Synbiotics: Can We Exploit Their Health Benefits in the Management of ITP?

As aforementioned, there is evidence that suggests a pathogenic involvement of dysbiosis in primary ITP (see Sect. 19.2.2). Dysbiosis has been linked to the development of several ailments, particularly cardiometabolic disorders, e.g., obesity, type 2 diabetes, the metabolic syndrome, cancer, and other non-communicable diseases (Pourrajab et al. 2020; Patterson et al. 2016; Ryan et al. 2017). In this regard, the potential health benefits of probiotics (live microorganisms administered with the aim of improving the health of a certain host), prebiotics (a substrate, e.g., dietary fiber, administered to a subject aiming that is to be employed by the host's microorganisms to generate health benefits), or synbiotics (a mixture of pre- and probiotics) have attracted the interest of the international community or researchers and have been explored in various disorders (Pourrajab et al. 2020; Patterson et al. 2016; Ryan et al. 2017; Hill et al. 2014; Gibson et al. 2017; Swanson et al. 2020). Several strains of probiotics, i.e., *Lactobacillus*, *Saccharomyces*, *Bifidobacterium*, *Streptococcus*, *Enterococcus*, *Pediococcus*, *Bacillus*, *Leuconostoc*, *Escherichia coli*, and others, prebiotics (dietary fibers), and synbiotics have displayed a myriad of health benefits in other non-hematological disorders and could be explored in the future management of ITP (Fijan 2014; Fatahi et al. 2021). However, further research is needed to investigate the safety of these natural products in the therapeutic armamentarium of ITP and to ensure that the administration of these compounds will not lead to the onset of secondary ITP or trigger/aggravate primary ITP.

19.6 Conclusions

Microbial pathogens play important roles in the development of ITP, particularly secondary ITP. Several of the microbial pathogens involved in the development of secondary ITP include, but are not limited to, *Helicobacter pylori*, HIV, HCV, HBV, and SARS-CoV-2. Alterations of the gut microbiota, as well as vaccination, can trigger the onset of ITP.

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Part VI

Microorganisms in Pathogenesis and Management of Autoimmune Eye Diseases

Microorganisms in Pathogenesis and Management of Autoimmune Uveitis

20

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Abstract

The gut microorganisms are recently recognized as essential organs of the human body. Dysbiosis of the microbiome is closely correlated with the pathogenesis of many autoimmune diseases, such as autoimmune uveitis. We summarized recent research results about the role of dysbiosis in autoimmune uveitis. These results suggest potential therapeutic strategies to treat this disease through antibiotics and probiotics.

Keywords

Gut microorganism · Autoimmune uveitis · Antigenic mimicry · Metabolism · Probiotics

20.1 Introduction

Autoimmune uveitis is non-infectious uveitis that can cause blindness (Forrester et al. 2018). Uveitis is common in young adults. Up to 25% of vision loss in developing nations and 10–15% of avoidable vision loss in developed nations are related to uveitis (Caspi 2010; Durrani et al. 2004). Autoimmune uveitis frequently occurs with other immune diseases or is the eye presentation of some systemic

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immune diseases, such as Behçet's disease and Vogt-Koyanagi-Harada disease (Shimizu et al. 2016; Horai and Caspi 2019). The exact mechanism of autoimmune uveitis remains elusive, but the imbalance between Th1/Th17effector T cells and regulatory T cells (Tregs) may play a role in this disease (Mochizuki et al. 2013). The crucial roles of gut organisms in the pathogenesis of uveitis have been suggested by recent clinical observations and animal models (Levy et al. 2017).

A complex group of symbiotic, commensal organisms live on the surface of the human body, such as the skin, mouth, intestine, airway, and conjunctiva. These complex communities of microorganisms that include bacteria, fungi, viruses, and other microbial and eukaryotic species usually do not hurt but are helpful (Belkaid and Hand 2014; Khan et al. 2019). The gut is the major interface to host microbes. Gut microbiota refers to microorganisms colonizing the intestinal tract, consisting of about 10^{14} microorganisms (Szablewski 2018). The gut microbiome can protect the host from pathogens, promote food digestion and nutrition absorption, and regulate the host's immune system (Shivaji 2019). Dysbiosis refers to unbalanced changes in the normal gut microbes (Robles Alonso and Guarner 2013). Dysbiosis can help pathogenic species invade, grow, disturb the immune system (Gritz and Bhandari 2015). Indeed, many studies have indicated a close relationship between dysbiosis and different diseases, such as ankylosing spondylitis (Ciccia et al. 2017; Wen et al. 2017), Graves' disease (Hou et al. 2021), inflammatory bowel disease (Gianchecchi and Fierabracci 2019; Kassam et al. 2018), multiple sclerosis (Zeng et al. 2019; Tsunoda 2017), rheumatoid arthritis (Gianchecchi and Fierabracci 2019), and more.

While microorganisms on other surfaces may also impact autoimmune uveitis such as ocular surface bacteria (Li et al. 2020), the gut microbiota is the most critical microorganism for autoimmune uveitis (Fu et al. 2021). This chapter thus focuses on recent findings regarding the gut microbiome in autoimmune uveitis and suggests ways to treat this disease by modifying intestinal microbes.

20.2 Correlations Between the Intestine Microbe and Autoimmune Uveitis

During the last 10 years, studies of uveitis patients and animal models discovered a significant correlation between the intestine microbe and uveitis. In addition, some immunosuppressants commonly used to treat autoimmune diseases also have antimicrobial functions.

20.2.1 Animal Models of Experimental Autoimmune Uveitis

Depleting the intestine microbe can reduce the severity of autoimmune uveitis in experimental mouse models (Heissigerova et al. 2016; Nakamura et al. 2016; Horai et al. 2015). Mouse models of induced and spontaneous experimental autoimmune uveitis (EAU) were the research system for these investigations. Active immunization with the inter-photoreceptor retinoid-binding protein (IRBP) can induce EAU in

B10.RIII or C57BL/6J mice (Horai and Caspi 2019). The R161H B10.RIII transgenic mouse is a spontaneous EAU model that expresses an IRBP-specific T cell receptor (TCR) transgene and has increased peripheral $CD4^+$ T cells specific to IRBP161-180 peptide (Horai and Caspi 2019).

The severity of induced EAU is higher in mice housed conventionally than germ-free (GF) housed C57BL/6J mice. The retina's infiltrating macrophages and T cells were reduced in GF mice, which also had a lower amount of IFN-γ and IL-17-producing T cells, but a higher amount of Treg cells in the eye-draining lymph nodes. These results indicated that the intestine microbiome is closely linked to EAU (Heissigerova et al. 2016). The severity of induced EAU in B10.RIII mice were greatly attenuated by oral broad-spectrum antibiotics (such as metronidazole and vancomycin), but intraperitoneal injection of these drugs had no effects (Nakamura et al. 2016). Similar effects were observed in C57BL/6J mice with induced EAU by orally delivered metronidazole and ciprofloxacin (Heissigerova et al. 2016). Conversely, oral feeding of IRT-5 or *Escherichia coli* Nissle 1917 (EcN) probiotics reduced the severity of induced EAU in C57BL/6J mice (Kim et al. 2017; Dusek et al. 2020). These observations supported the notion that the intestine microbiome is closely linked to EAU. The R161H spontaneous EAU was also linked to the intestine microbiome, as hosting R161H mice under germ-free conditions or prenatal treatment with broad-spectrum antibiotics can reduce the disease progression and decrease the number of intestine IRBP-specific T cells (Horai et al. 2015).

20.2.2 Clinical Observation of Uveitis Patients

The microbiota was also different between uveitis patients to healthy people. Comparing the gut microbiota of 12 uveitis patients with Behçet's disease (BD) and 12 healthy controls revealed that *Bifidobacterium* and *Eggerthella* increased. At the same time, *Megamonas* and *Prevotella* decreased in BD uveitis patients (Shimizu et al. 2016). Even though acute anterior uveitis (AAU) patients had a normal gut microbiota composition, their fecal metabolic phenotype changed significantly. There were seven fecal metabolites increased in AAU patients (Huang et al. 2018). Active VKH patients had more gram-negative bacteria (*Paraprevotella* spp.) but less butyrate or lactate-producing bacteria and methanogens. Immunosuppressive treatment can reduce these differences. Good response to immunosuppresant was related to *Bacteroides* sp.2.1.33B, *Paraprevotella clara*, *Alistipes finegoldii*, and *Eubacterium* (Ye et al. 2020). These observations are consistent with the results from EAU mouse models. Interestingly, fecal transplantation from BD patients (Ye et al. 2018) or patients with active VKH disease (Ye et al. 2020) significantly increased the expression of IL-17 and IFN-γ and deteriorated EAU phenotypes in B10.RIII mice.

The diversity and abundance of gut microbiota decreased in a cohort with 13 uveitis patients (including idiopathic and autoimmune uveitis) (Kalyana Chakravarthy et al. 2018). Specifically, the diversity of several anti-inflammatory microbes (*Faecalibacterium*, *Bacteroides*, *Lachnospira*, and *Ruminococcus*)

decreased. At the same time, the pro-inflammatory *Prevotella copri* and pathogenic bacteria *Streptococcus* increased in this uveitis cohort (Kalyana Chakravarthy et al. 2018). The diversity and abundance of gut fungal species also decreased in this cohort (Jayasudha et al. 2019). Opportunistic fungal pathogens were enriched in the uveitis patients, while several fungal genera with anti-inflammatory or anti-pathogenic properties were enriched in the healthy controls (Jayasudha et al. 2019).

20.2.3 Immunosuppressive Medications Can Affect Gut Microbes

Immunosuppressive medications can improve the dysbiosis of VKH patients. The underlying mechanism of this observation may be related to their direct effect on microbiota (Ye et al. 2020). Disease-modifying anti-rheumatic drugs (DMARDs), including azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), and cyclosporine A (CsA) are commonly applied to rheumatoid arthritis and other autoimmune diseases (Rossi et al. 2019). All these drugs have anti-microbial functions (Jones 2020).

AZA is widely used to treat inflammatory bowel diseases (IBD) and uveitis (Adam et al. 2018; Tran and Tsui 2021). The active form of AZA is 6-mercapto-purine, which can inhibit the synthesis of DNA and RNA. AZA can directly suppress *Campylobacter concisus*, *Escherichia coli*, and *Mycobacterium avium paratuberculosis*. AZA can also affect the secretion of the extracellular matrix of *E. coli* (Liu et al. 2017; Antoniani et al. 2013). MTX is an analogue of folic acid and can interfer with purine and pyrimidine metabolism. Thus, MTX can also suppress the synthesis of DNA and RNA and inhibit *Staphylococcus aureus* (Kruszewska et al. 2010). Refractory uveitis can be treated with MMF (Kilmartin et al. 1998). MMF can interrupt guanosine synthesis by inhibiting inosine monophosphate dehydrogenase. MMF inhibits the synthesis of microbial DNA and RNA and thus has a wide range of anti-microbial property (Jones 2020). CsA is derived from fungi and has direct effects against *Candida albicans* and *Cryptococcus neoformans* as it can interfere with fungal metabolism. CsA can also bind with cyclophilin, thus inhibit intracellular multiplication of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) (Peel and Scribner 2013). As these drugs are commonly used for uveitis, it is possible their effects are partially mediated by regulating gut microbes (Heissigerova et al. 2016; Nakamura et al. 2016; Horai et al. 2015).

20.3 How Gut Microbiota Affect the Development of Autoimmune Uveitis

Four major mechanisms are proposed: antigenic mimicry, disruption of gut immune homeostasis, loss of the intestinal barrier, and intestine microbial metabolites (Fig. 20.1).

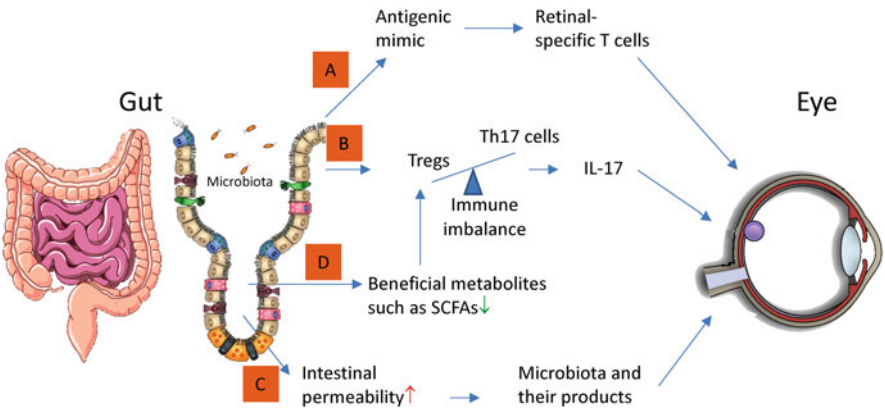

Fig. 20.1 Dysbiosis of the gut microbiome induces autoimmune uveitis through four potential mechanisms. (**a**) Antigenic mimicry: Antigenic mimics from the intestine microbiota activate retinal-specific T cells, which can enter the eye to induce uveitis. (**b**) Disruption of gut immune homeostasis: Th17 cells/Tregs cells ratio is increased, secretion of IL-17 is increased. (**c**) Loss of the intestinal barrier: Microbes and their biological components (e.g. LPS and β-glucan) can enter the vascular circulation and enter the eye through the leaking intestine. If the uvea stops them, they can induce uveitis. (**d**) Metabolic pathway: Dysbiosis reduces the beneficial anti-inflammatory metabolites such as SCFAs

20.3.1 Antigenic Mimicry

The similarity between different antigens can cause cross-reactivity, called molecular or antigenic mimicry. Such similarities can be among amino acid sequences, nucleotide sequences, or protein conformations (Miraglia and Colla 2019). Cross-reactivity between intestine microorganism products and self-antigens can produce autoreactive T cells and induce autoimmunity (Rojas et al. 2018; Avni and Koren 2018; Wildner and Diedrichs-Möhring 2020). Microbial antigen mimicry was first suggested as the trigger of EAU in mouse models (Horai et al. 2015). T cells from spontaneous EAU R161H mice were activated in vitro by intestinal contents. Adoptive transfer of these activated T cells can induce EAU in many naïve wild-type mice within 6–10 days (Horai et al. 2015).

Soluble retinal antigen (S-Ag), also known as rod arrestin, is a major component of rod outer segments. S-Ag can induce EAU in susceptible hosts (de Smet et al. 2001). Several peptides from microbes with similarity to S-Ag can induce EDU. For instance, six amino acids of a synthetic peptide of *E. coli* protein are similar to S-Ag (aa303–320); this peptide can induce EAU in Lewis rats (Singh et al. 1989). Similarly, peptides from several viruses (including Hepatitis B virus, Baboon virus, murine leukemia virus, murine sarcoma virus, and rotavirus) were identified with similarity to S-Ag and also induced EAU in Lewis rats (Wildner and Diedrichs-Möhring 2003, 2020; Singh et al. 1990). These data suggested that antigenic mimicry of microorganism products can induce autoimmune uveitis.

20.3.2 Disruption of Gut Immune Homeostasis

The gut-associated lymphoid tissues (GALT) are the critical antigen sampling and adaptive immune inductive sites within the intestinal wall (Mörbe et al. 2021). The GALT has many T cell populations, including pro-inflammation helper T (Th) cells and anti-inflammation regulatory T cells (Tregs) (Okeke and Uzonna 2019). T helper cells include Th1, Th2, and Th17 cells. Th17 cells are a unique $CD4^+$ T helper subset characterized by IL-17 production promoting tissue inflammation. Th17 cells are critical in protecting mucosal surfaces against microbial pathogens and are major contributors to autoimmune inflammation (Pandiyan et al. 2019; Bettelli et al. 2007; Omenetti and Pizarro 2015). Tregs are dedicated suppressors of diverse immune responses and inflammation and central keepers of peripheral tolerance (Omenetti and Pizarro 2015). In the GALT, Th17 and Tregs cells are in a dynamic balance to maintain the immune homeostasis of the intestine mucosa. Gut microbiotais is crucial for maintaining the balance between Th17/Tregs (Omenetti and Pizarro 2015). The dysbiosis could increase Th17 cells and reduce Tregs production (Zhuang et al. 2017). The imbalance of Th17/Tregs is implicated in the development of autoimmune uveitis (Mochizuki et al. 2013) and is indispensable to the pathogenesis of Behcet's disease (Leccese and Alpsoy 2019). Oral broad-spectrum antibiotics can increase $FOXP3^+$ Tregs and reduce Th17 and inflammatory cytokines in the GALT and retina, thus reducing the severity of EAU in mice (Nakamura et al. 2016).

20.3.3 Loss of the Intestinal Barrier

The intestinal mucosa is exposed to many external antigens and commensal microbes. The intestine thus becomes a barrier tissue with a monolayer of intestinal epithelial cells. Dysbiosis, especially the loss of beneficial species, has been implicated in mucosal barrier dysfunction and increased intestinal permeability (Kinashi and Hase 2021). Leaky gut has been reported in patients with ankylosing spondylitis (Ciccia et al. 2017) and animal models of autoimmune diseases (Levy et al. 2017). Similarly, EAU mouse models have leaky gut with morphological changes of intestinal inflammation and increased intestinal permeability (Janowitz et al. 2019). Microbes and their biological components, such as lipopolysaccharide (LPS) and β-glucan can enter the blood circulation through a leaking intestinal tract. If uvea stops them, they can trigger immune responses that cause uveitis (Rosenbaum and Asquith 2018; Rosenbaum et al. 2016).

20.3.4 Metabolic Pathway

The commensal microbiota produces various fermentation products, such as indoles and short-chain fatty acids (SCFA), including primarily acetic acid, propionic acid, and butyric acid. These metabolites substantially impact host physiological functions through metabolic reprogramming, epigenetic modifications, and the activation of

specific receptors like G protein-coupled receptors (GPRs) (Kinashi and Hase 2021). SCFAs are beneficial to the host and protective in the animal models of inflammatory disease. For instance, SCFA butyrate can augment the intestine barrier by inducing the hypoxia response. It upregulates claudin-1 and occludin expression in a Hif-1-dependent manner, conferring resistance to barrier disruption and bacterial translocation upon infection with *Clostridium difficile* (Fachi et al. 2019). SCFAs can increase Tregs and reduce effector T cells, thus ameliorating uveitis. Indeed, exogenous SCFAs can reduce the severity of EAU in mice (Nakamura et al. 2017). AAU patients have unique metabolic profiles in the gut, with higher expression of seven metabolites (including 6-deoxy-D-glucose 1, linoleic acid, N-Acetyl-beta-D-mannosamine 3, shikimic acid, azelaic acid, isomaltose 1 and palmitoleic acid) (Huang et al. 2018). However, if these seven metabolites are related to the pathogenesis of AAU is unknown.

20.4 Targeting the Gut Microbiota to Treat Uveitis

Dysbiosisis is closely related to the pathogenesis of autoimmune uveitis, which provides excellent therapeutic options, including antibiotics or probiotics.

20.4.1 Antibiotics

Obviously, antibiotics can change the intestine microbiota. It was shown that oral antibiotics ameliorated the severity of inducible EAU in mice (Nakamura et al. 2016). Oral broad-spectrum antibiotics from 1 week prior to immune induction of EAU in conventionally housed mice could protect them from severe autoimmune inflammation (Heissigerova et al. 2016). However, currently, there is no clinical data on using antibiotics in patients with autoimmune uveitis.

20.4.2 Probiotics

Probiotics are microbial preparations that deliver bacteria beneficial to the host by improving the intestine barrier and promoting a balanced immune function in GALT (Lin 2019). IRT-5 probiotics have *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*. Preclinical studies of probiotics IRT-5 on the EAU mouse model suggested that IRT-5 can regulate ocular autoimmunity and prevent EAU (Kim et al. 2017). Recently an 18-year-old woman with unilateral AAU in the right eye was treated with a probiotic cocktail (to be taken every day in the morning for 1 year) and standard topical treatment protocol (1% dexamethasone phosphate 4 times daily and 1% atropine 2 times daily) for 3 years. The probiotic cocktail is composed of a single dose of $\geq 1 \times 10^9$ live cells of *Bifidobacterium lactis BL04* (DSM 23233), $\geq 1 \times 10^9$ live cells of *Bifidobacterium bifidum BB01* (DSM 22892), and $\geq 1 \times 10^9$ live cells of

Bifidobacterium breve BR03 (DSM 16604) (Probiotical S.p.A., Novara, Italy). During the treatment period, the ocular inflammation decreased, and the best-corrected visual acuity increased, and the steroids and atropine were discontinued for the following months. This result demonstrated that probiotics could reduce recurrences of AAU (Napolitano et al. 2021). However, this needs to be confirmed in randomized controlled clinical trials.

20.5 Conclusion

An essential role of intestine microbes in the pathogenesis of autoimmune uveitis has emerged recently. EAU animal models demonstrated that depleting the intestine microbiota can reduce the severity of autoimmune uveitis. The composition of the gut microbiota was often changed in uveitis patient cohorts. Commonly used immunosuppressive medications for the treatment of uveitis have some antimicrobial functions. Dysbiosis may induce autoimmune uveitis through antigenic mimicry, imbalance of Th17/Tregs cells in the gut, loss of the gut barrier, and reducing beneficial microbial metabolites. Potential therapeutic means targeting gut microbes include antibiotics and probiotics. Further studies will elucidate the molecular pathways linking gut and uvea autoimmunity. The gut microbial composition of autoimmune uveitis patients needs to be determined in more cohorts and more geographic locations. The effects of different probiotic formulas on the EAU mouse model and patients need to be investigated.

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Role of Microorganisms in Pathogenesis and Management of Autoimmune Retinopathy (AIR)

21

Gazal Patnaik and Jyotirmay Biswas

Abstract

Autoimmune retinopathies (AIRs) are a group of autoantibody-mediated retinal degenerations characterized by progressive visual deterioration, visual field loss, abnormal electroretinography (ERG) with a normal looking retina or a minimally apparent structural changes in the retina. It is characterized by the presence of antiretinal antibodies (ARAs) causing photoreceptor dysfunction. AIR is an immunologic disorder whereby retinal antigens are recognized aberrantly as autoantigens, leading to retinal degeneration as evidenced by basic immunological studies. However, exact underlying pathomechanism remains elusive. Most of the evidences are from experimental animal models. The incidence as well as the severity of the disease decreases under a germ-free environment which further strengthens the hypothesis of microbiota being a trigger for the autoimmune diseases. Four mechanisms triggering the gut-eye axis for causing intraocular inflammation have been hypothesized including antigenic (molecular) mimicry, destruction of intestinal barrier, increased intestinal permeability, microbial metabolites, dysbiosis. No standardized protocol has yet been established for patients with AIR. Considering a pivotal role of gut microbiota in autoimmune uveitis, four main therapeutic approaches are developed. This includes antibiotics, probiotics, dietary modifications, and fecal microbiota transplantation (FMT). Methionine aminopeptidase 2 (MetAP2) inhibitors like lodamine have shown to have significantly reduced the inflammatory cell

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infiltration and granuloma formation. The intestinal microbiome thus represents a salient potential target for therapeutic modulation to treat these potentially blinding conditions. Prospective studies are required to analyze the proposed experimental therapeutic approaches for a clinical implication.

Keywords

Autoimmune retinopathy · Probiotics · Lodamine · Fecal microbiota transplantation · Microbiome

21.1 Introduction

Uveal tract comprises the iris, ciliary body, and choroid. Depending upon the structure involved in the inflammatory process, uveitis is either anterior (iritis, iridocyclitis), intermediate (vitritis), and posterior uveitis (choroiditis) or panuveitis involving the entire uveal tract. This inflammatory process might extend to involve the adjacent structures like retina (retinal vasculitis, retinitis, retinochoroiditis, or chorioretinitis) or optic nerve (optic neuritis). This often affects the working strata of the population with a median age of around 35 years, forming an economical burden as well. Significant visual loss can lead to legal blindness and is reported in around 35% of cases. However, this is a preventable cause of blindness accounting for nearly 25% and 10–15% of preventable blindness in the developing and the developed countries, respectively (Caspi 2010; Durrani et al. 2004).

Uveitis is the inflammation of the uveal ocular coat. It is one of the dreaded sights—threatening ocular disorders. The disease is found responsible for around 10–15% of the visual morbidity worldwide and is one of the leading causes of blindness in the developed countries (Caspi 2010; Miserocchi et al. 2013). Another worrisome factor is the affection of the disease for the middle aged working population, affecting the economic and the social strata as well. Uveitis could be due to infection, inflammation, or even immune-related diseases. Immune-related mechanisms could also be a contributory factor in both the infectious and non-infectious causes, mainly associated with the latter. Uveitis is caused or triggered due to various ocular and systemic etiologies. This chapter focuses mainly on the autoimmune retinopathy (AIR).

Autoimmune retinopathies (AIRs) are a group of autoantibody-mediated retinal degenerations characterized by progressive visual deterioration, visual field loss, abnormal electroretinography (ERG) with a normal looking retina, or a minimally apparent structural changes in the retina (Adamus et al. 2006). It is characterized by the presence of antiretinal antibodies (ARAs) causing photoreceptor dysfunction. AIRs are broadly categorized into paraneoplastic AIR (pAIR) and non-paraneoplastic AIR (npAIR). pAIR further comprises cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). Until now, over 100 cases have been reported in the literature, still the diagnosis and management of AIR remain challenging owing to a lack of standardized diagnostic criteria and

identification of ARAs with certainty (Adamus et al. 2004; Adamus 2009; Ferreyra et al. 2009; Larson et al. 2010).

21.2 Pathophysiology of AIR

AIR is an immunologic disorder whereby retinal antigens are recognized aberrantly as autoantigens, leading to retinal degeneration as evidenced by basic immunological studies. Diagnosis, thereby, depends on the presence of ARAs in the setting of clinical evidence of retinal degeneration. The exact role of ARAs in the pathogenesis of AIR is not completely understood. It is only speculated that they are cytotoxic to retinal cells through apoptotic mechanisms involving internalization of antibodies, caspase pathways, and calcium influx (Adamus 2003; Adamus et al. 2004; Magrys et al. 2007). ARAs detection could also precede the detection of tumors and therefore, it is important to investigate for underlying malignancy. It is proposed that the tumor cells aberrantly express proteins similar to those normally expressed by the retinal cells, leading to cellular mimicry. However, the exact role of cell-mediated immunity remains unresolved and needs further studies (Patnaik et al. 2020).

A change in the type of ARA has also been noticed in a few patients. The phenomenon is known as the epitope spreading (Dot et al. 2005). The changing antibodies might increase the pathogenicity and the severity of the disease. Still the cause of this epitope spread is unknown.

Autoimmune uveitis (AIU) could affect only the anterior uveal portion causing iritis or iridocyclitis, or it may even affect the retinal structures causing autoimmune retinopathy (AIR). AIU can also affect the entire uveal tract as in Vogt-Koyanagi-Harada (VKH) disease, sarcoidosis in the form of panuveitis. These have been associated with various human leukocyte antigen (HLA) haplotypes, namely HLA-DR4, HLA-B27, HLA-B5, HLA-A29, and so on, further supporting the autoimmune basis.

Although ocular structures are immune-privileged, various autoimmune mechanisms are involved in triggering and affecting specific retinal proteins such as interphotoreceptor retinoid protein (IRBP) and retinal arrestin. These protein molecules are expressed in the photoreceptor cells and are involved in the visual pathway.

21.3 The Gut Microbiota

A group of microorganisms in a specific environment together are called microbiota (Marchesi and Ravel 2015). Gut microbiota comprises several kinds of microorganisms inhabiting the gastrointestinal tract (GIT). Microbiome refers to the microbes, including all kinds of bacteria, fungi, protozoa, and viruses. However, some refer to the term to sum total of the genes and the genomes along with their

metabolites and the host microenvironment (Whiteside et al. 2015). This collective genome is nearly 100 times the size of the human genome (Szablewski 2018).

The human gut microbiota contains about 100 trillion microorganisms involved in various metabolic activities. It has a unique constitute for every individual and has also been implicated for genetic profiling (O'Hara and Shanahan 2006; Thursby and Juge 2017). The constitute, however, depends upon various modifiable factors such as the lifestyle, dietary habits, and physical activities (Rinninella et al. 2019). The microbiome system is a dynamic ecosystem constantly evolving since birth, fine-tuning itself and maintaining homeostatic balance with the hosts' immune system. Thereby, the gut microbiome is governed by various factors like diet, medications, disease as well as by the innate and the adaptive immune pathways (Gritz and Bhandari 2015). Any imbalance in this ever-evolving system affecting the gut microbes composition refers to dysbiosis (Robles Alonso and Guarner 2013). This imbalance favors invasion and growth of the harmful pathogenic microorganisms with the potential of causing illness and affecting the immune systems (Gritz and Bhandari 2015). Passive passengers in the past, now, gut microbiota have been found to be actively involved in the maintenance of the immune system (Vrancken et al. 2019).

This provoked an increasing interest among the scientist to further analyze this complex interaction between the innate, adaptive immune systems and the gut microbiome, demonstrating a connection in various autoimmune disorders like rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, dry eye, diabetic retinopathy, age-related macular degeneration, glaucoma and inflammatory bowel disease (Beli et al. 2018; Cavuoto et al. 2019; Chen et al. 2018; Ciccia et al. 2017; Doulberis et al. 2019; Gianchecchi and Fierabracci 2019; Kassam et al. 2018; Rinninella et al. 2018; Rowan et al. 2017; Trujillo-Vargas et al. 2019; Tsunoda 2017; Wen et al. 2017; Zeng et al. 2019).

The Human Microbiome Project has described various reference genomes responsible for the composition of the microbiota, especially 16S rRNA sequencing. This, in turn, helps to distinguish different bacterial genera (Knight et al. 2017). Proliferation of certain bacterial colonies has been found to be beneficial. For example, increase in *Lactobacillus* spp. has the potential to reduce neutrophil extracellular traps and *B. fragilis* has protective actions against autoimmune disorders with the help of its polysaccharide capsule (Lin 2018).

21.4 The Gut–Retina Axis

Recent research has accumulated enough evidence for the presence of a gut–brain axis, affecting central nervous system (CNS) development and cognitive behavior (Gareau 2016; Sampson and Mazmanian 2015). Gut microbiota has been implicated in various diseases of CNS (Carabotti et al. 2015; Colpitts et al. 2017; Wekerle 2016). With this development, there was an inclination to study any possibility of gut–retina axis as neural retina is an embryonic outpouching of the optic fissure of the developing brain. Additionally, the role of gut microbiota was found to be a

regulatory factor for ocular secretory IgA levels protecting the ocular mucosal surface (Kugadas et al. 2017). Subsequently, research was extended towards various retinal disorders, mainly the age-related macular degeneration (ARMD). Gut microbiota-derived metabolites like serotonin are found to be protective against ARMD (Rowan et al. 2017). Induction of innate immune response by the intestinal microbiota leads to post-natal development of the intestinal stability, secondary lymphoid system development and influences the adaptive immune responses (Atarashi et al. 2011; Ivanov et al. 2009; Picchianti-Diamanti et al. 2017; Rosenbaum and Asquith 2018; Round and Mazmanian 2010; Smith et al. 2013; Tan et al. 2016).

Further extension of this experimental research is required to establish the bi-directionality of the gut–retina axis and its implication in intraocular inflammatory disorders. However, the exact role and implications of the gut microbiome need to be studied in detail to clarify its role in the gut–eye axis. The link between the gut microbiome and uveitis has been first studied in HLA-B27-positive transgenic rat models. Upon observation of a significant difference in the bacterial composition in the affected rat and control normal group, an association between the diet and chronic uveitis was considered (Huang et al. 2018).

21.5 Experimental Autoimmune Uveitis (EAU)

Most of the evidence comes from the germ-free (GF) mouse models. The incidence as well as the severity of the disease decreases under a GF environment which further strengthens the hypothesis of microbiota being a trigger for the autoimmune diseases (Lee et al. 2011; Reháková et al. 2000; Vieira et al. 2014; Wen et al. 2008; Wu et al. 2010). However, the extrapolation of this link to causation of uveitis happened recently. Further supportive evidence comes from the antimicrobial properties of the immunosuppressive agents commonly used for the treatment of autoimmune disorders (Xiangyu et al. 2021).

Various animal models are designed to study different hypotheses. Broadly, two types of experimental mouse models are available for research purposes including induced EAU (IEAU) and spontaneous EAU models (SEAU). IEAU is generated by active immunization with CFA-emulsified IRBP protein along with a combination of mineral oil and heat-killed MTB with or without pertussis toxin. SEAU mouse model has the tendency to express IRBP-specific T-cell receptor (TCR) transgene on the B10.RIII genetic background (Horai and Caspi 2019). The classical of these is the EAU. EAU is induced by emulsification of the IRBP protein in complete Freund's adjuvant (CFA), a mixture of mineral oil with heat-killed *Mycobacterium tuberculosis* (MTB).

Different mice strains have varied susceptibility to the immunization regimen and the development of ocular inflammation. Some strains need an additional toxin like pertussis toxin to induce AIU. However, some mice strains like the B10.RIII are highly susceptible to the classical CFA-MTB toxin. The additional need for the bacterial toxin is to induce a pro-inflammatory milieu activating the innate immune

system that would further induce adaptive immune responses triggering the effector pathways (Horai and Caspi 2010).

21.6 Spontaneous Autoimmune Uveitis Model (SAIU)

SAIU is a model of EAU which is independent of gut microbiota and functioning. The AIRE protein is expressed in the medullary thymic epithelial cells, functioning as a transcription factor controlling the expression of tissue-specific proteins like sequestered retinal proteins. This negative selection of the autoreactive T-cells by the thymic protein forms the central tolerance mechanism of the innate immunity. Dysfunction or deletion of this AIRE protein can, therefore, lead to autoimmunity towards various infectious diseases (Anderson et al. 2002; Proekt et al. 2016). The autoimmunity in this mouse model depends on the genetic makeup of the mice. A characteristic of AIRE knockout mice is their recognition of IRBP retinal protein as pathogenic, although this has the potential to select T-cells against other retinal proteins like arrestin.

21.6.1 Specific Pathogen Free (SPF) and Germ Free (GF) Mice Models

This mice model is unique in its ability of non-dependence on the commensal microbiota. The autoimmune responses developed in the mice under SPF and GF environments are similar in all the organs like the eye, lungs, and pancreas (Gray et al. 2007). Various other possible combinations of the genetic defects have been experimented upon. We would not go into details of the various experimental AIRE allele models. However, in most of the models the eye was found to be selectively affected in double mutant mice. The spontaneous intraocular inflammation developed in the models was unaffected by the broad-spectrum antibiotics, further strengthening its non-dependence on the gut microbiota (Proekt et al. 2016). However, there was increased retinal specific T-cells in all the varied models with different TCR affinity.

GF-mouse models produce lesser numbers of infiltrating macrophages and T-cells producing IFN-γ and IL-17. They, however, produce greater numbers of Treg cells as compared to EAU. This supports a close interaction between the gut microbiome and uveitis (Heissigerova et al. 2016). Further strengthening this observation is the response of induced uveitis in the mouse models towards the oral antibiotics treatment (broad-spectrum antibiotics like metronidazole, ciprofloxacin, and vancomycin) (Nakamura et al. 2016). Probiotics administration, consisting of five microbes, namely *Lactobacillus* casei, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*, alters the clinical severity and features of uveitis (Kim et al. 2017). Treatment of R161H mice before birth with a combination of broad-spectrum antibiotics has shown significant reduction in numbers of IRBP-specific T-cells in the intestinal lamina propria (Horai et al. 2015).

21.7 Clinical Implications of EAU Models

Trigger of the autoimmunity basically depends upon an imbalance between the autoreactive effector T-cells and the Treg cells. The pathogenic T-cells consist mainly of the helper T-cells such as Th1 and Th17 lymphocytes, whereas Tregs form the regulatory types of T-cells (Mochizuki et al. 2013; Levy et al. 2017). Geographical disparity among different ethnic groups for a particular disease and predilection of a particular autoimmune disease for a specific region has been well known. However, recent comparison of the microbial colonies led to the observation of a difference in the gut microbiome also. An increase in *Bifidobacterium* and *Eggerthella* with a decrease in *Megamonas* and *Prevotella* has been noticed in the Behcets disease (BD) of Japanese patients (Shimizu et al. 2016). This dysbiosis was then thought of as an association with the pathogenesis of BD. Another group studied the microbiota in the Chinese population. They could not find any difference in the gut microbiome; however, a difference was noticed in the fecal metabolic phenotypes in the acute anterior uveitis (AAU) group as compared to the control group (Huang et al. 2018). FMT from patients with BD were transplanted into a B10. RIII uveitis-prone mice model. An increase in the production of the inflammatory cytokines, mainly IL-17 and IFN-γ, with an exacerbation of the EAU was noticed (Ye et al. 2018, 2020).

These observations support the potential causation between dysbiosis and autoimmune uveitis. A detailed microbiota analysis in patients with VKH has established two microbial marker profiles for predicting the effectiveness of immunosuppressive agents in the VKH patients. *Bacteroides* sp.2.1.33B, *Paraprevotella clara*, *Alistipes finegoldii*, and *Eubacterium eligens* have been associated with a better response to the immunosuppressive treatment (Ye et al. 2020). A depletion in the lactate and butyrate-producing bacteria is also noticed in the active VKH patients.

The role of T-cell immunity has been implicated in many of the autoimmune uveitic conditions, through many experimental as well as clinical researches. However, some scientists claim the role of humoral immunity as well (Mochizuki et al. 1985; Merryman et al. 1987; Marak et al. 1979; De Kozak et al. 1981; Caspi et al. 1986). Whereas few other groups disagreed with any possible role of either cell-mediated or humoral immune system acting against retinal antigens such as the human S-antigen and IRBP. An extensive research on the role of autoimmunity for onchocercal chorioretinopathy did not show any cellular or humoral response against the retinal antigens as compared to the endemic controls. They reverted back to the age-old concept of direct invasion of the Onchocercal microfilariae or their toxins in the pathomechanism of chorioretinopathy (Van der Lelij et al. 1990). Histological evidence also has reported microfilariae in both the retina and the choroid (Neumann and Gunders 1973; Paul and Zimmerman 1970; Rodger and Chir 1960). Antiprotozoal agents like diethylcarbamazine can provoke new lesions or aggravate the existing retinal lesions by killing the live microfilariae. This further supports the hypothesis of the role of live microbial organisms rather than autoimmunity (Anderson and Fuglsang 1976).

21.8 Translational Science

Apart from the different microbiota makeup in every individual, the onset and the severity of AIR vary among populations. Genetic polymorphisms altering protein functioning have also been studied in this regard. Epigenetic modifications explain the role of environmental signals regulating the gene transcriptions. Environmental triggers affect the cellular response when extracellular signals are translocated into the nucleus, thereby leading to epigenetic reprogramming. Therefore, identification of such extracellular environmental triggering factors involved in impairing cellular function becomes essential for analyzing the inflammatory process in AIR (Wen et al. 2018).

Hypomethylation of the genetic factors in the retinal pigment epithelium and the choroid causes an increased generation of the pro-inflammatory cytokines like IFN-γ and IL-17. Upregulation of miRNA-223 causes dysbiosis, activation of T-cells and myeloid dendritic cells (DCs), promoting inflammation. These miRNAs are associated with an increased signaling cascade like mitogen-activated protein kinase (MAPK), forkhead box (FOXO), and vascular endothelial growth factor (VEGF). A comparison between the levels of miRNA in patients with inflammation and healthy controls found a significant level of this protein in the affected individuals (Verhagen et al. 2018; Qiu et al. 2018).

Furthermore, intravitreal injection of human immunoglobulin G (IgG) from MAR patients into the eyes of monkeys resulted in similar ERG waveforms characteristic of MAR in an in vivo experiment. They showed a reduced dark-adapted b-wave accompanied by a normal a-wave suggesting disruption of ON-bipolar cell signaling (Okel et al. 1995; Lei et al. 2000). Another experimental study on mice recognized transient receptor potential cation channel subfamily M member 1 (TRPM1) as essential for ON-bipolar cell function, and TRPM1 is also found to be expressed by melanocytes (SL1). TRPM1 is identified as the target antigen against which ARAs have been identified in some MAR patients (Dalal et al. 2013; Xiong et al. 2013).

21.9 Commensal Microbiota as a Trigger of Uveitis

Commensal microbiota is a group of microorganisms inhabiting all the exposed surfaces of the human body. They are highly colonized and outnumber all human cells by tenfold. It was hypothesized that the triggering autoreactive cells for a specific autoimmune inflammatory condition need to pass through the gut to be activated. However, this hypothesis of a peripheral activation of the immune cells seems debatable provided the fact of sequestered retinal antigen in an immune-privileged state. For AIR, specific retinal antigens in the eye as well as in the retina-specific lymphocytes need to be activated to be able to breach the blood–retinal barrier. Various observations are made from the experimental mouse models supporting the above hypothesis.

The uveitis-specific T-cells are observed to be activated in the intestinal lamina propria as early as 17 days from induction EAU, before the onset of clinically apparent uveitis. Furthermore, there was an ameliorating effect seen over the severity of uveitis following depletion in the commensal microbiota when a combination of enteric broad-spectrum antibiotics was administered before birth of the R161H mouse model. Similar results were noticed in the mice under GF condition. Initiation of the uveitic process was associated with an increase in Th17 cells in the intestinal lamina propria, whereas a decrease in the Th17 cells was seen in the GF-mouse model. However, a co-housing of the GF-mouse model with SPF mice led to an onset of autoimmune uveitis. Above observations strongly laid the basis for role of commensal gut microbiota in the pathophysiology of AIR (Zarate-Blades et al. 2017; Horai et al. 2015). However, uveitis has been observed to develop in the GF-mouse models as well over the course of time, delayed in onset with a reduced severity as compared to the SPF models. Therefore, although the microbiota does have a role as stimulus for AIR, it is not the sole trigger. The gut microbiota, therefore, can have a modulatory effect in spontaneous uveitis as compared to the sole causative role in the induced—EAU (Nakamura et al. 2016). A reduction in the Treg cells was observed in the EAU following exposure to broad-spectrum antibiotics. A single treatment was found effective in controlling the inflammation in induced EAU. Conversely, no effects were seen on the number of Tregs in the lamina propria of the spontaneous uveitis-mouse models following a single antibiotic treatment. All four broad-spectrum antibiotics were required to prevent induction of spontaneous uveitis. This raised the probability of involvement of a complex diverse group of commensals for modulating the disease (Zarate-Blades et al. 2017).

Rosenbaum and group had hypothesized four mechanisms that trigger the gut–eye axis for causing intraocular inflammation (Rosenbaum and Asquith 2018). First, dysbiosis causes either an alteration in the intestinal homeostasis or in the local intestinal immune homeostasis, which leads to migration of bacterial products and activated immune cells to remote sites. This, in turn, reduces the activation of the immune cells, promoting a pro-inflammatory milieu. Second, molecular mimicry acts by reducing the threshold of tolerance towards the normally sequestered retinal antigens. However, peripheral retina-specific T-cells need to be activated to traverse through a breached blood–retinal barrier in order to enter the retinal tissues for triggering the autoimmune process.

21.10 Mechanism for Dybiosis Causing AIR

21.10.1 Antigenic (Molecular) Mimicry

Cross-reactivity between the gut microbiota and the sequestered retinal antigens generating autoreactive T-cells is known as antigenic or molecular mimicry (Rojas et al. 2018; Avni and Koren 2018). Through mimicking host antigens, microbial organisms tend to escape the immune pathways. Similarities have been found among

the amino acid sequence, nucleotide sequence, and the protein structures of their cell wall (Miraglia and Colla 2019).

This mechanism of autoimmunity is yet to be explored in the fields of uveitis. However, many other autoimmune conditions have been studied for involvement of such mechanisms in their pathogenesis. Adenosine triphosphate-binding cassette transporter permease (ABC-TP) expressed by *Clostridium perfringens* has around 90% homology with the amino acid sequence of the aquaporin 4 (AQP4) T-cell epitope. The cross-reactivity between both these proteins suggests a role of molecular mimicry in the pathogenesis of neuromyelitis optica (NMO), an immune-mediated demyelinating disorder of optic nerve and spinal cord (Cree et al. 2016; Varrin-Doyer et al. 2012). Similar observations have been made in patients with systemic lupus erythematosus (SLE). Natural commensals in the skin, oral mucosa, and the gut, especially *Propionibacterium propionicum* and *Bacteroides thetaiotaomicron*, have homology with the RNA-binding Ro60 autoantigen. This antigenic mimicry activates Ro60-specific CD4 memory T-cells in the SLE patients triggering the autoimmune disease (Avni and Koren 2018; Collison 2018; Greiling et al. 2018). Induction of IRBP retinal antigens via non-cognate microbial antigens through retina antigen-specific clonotypic TCR can activate AIR (Horai et al. 2015).

21.10.2 Loss of Intestinal Immune Homeostasis (Imbalance Between Th17 and Tregs)

The gut-associated lymphoid tissue (GALT), upon exposure to microbes, presents the potential pathogens to the T-helper cells, mainly Th17. Stimulation of Th17 cells leads to their proliferation and secretion of inflammatory cytokines like IL-17. To counteract this pro-inflammatory milieu, Tregs inhibit the exaggerated immune response, thereby preventing persistent inflammation. A balance exists between the Th17 and Tregs, under normal circumstances, and is under a constant dynamic correlation maintaining the gut microbial homeostasis (O'Hara and Shanahan 2006).

Any alteration in the composition of the gut microbiome, known as dysbiosis, can lead to a dysregulation of the gut immune homeostasis. A breakdown of the Th17/Treg balance lowers the threshold for immune system activation. This stimulates an increased proliferation of Th17 cells and a simultaneous decrease in the Tregs proliferation, provoking various intestinal as well as extraintestinal autoimmune disorders (Zhuang et al. 2017). Similar observation regarding the Th17/Treg balance has been noticed in the models for BD (Leccese and Alpsoy 2019). Not only does the decrease in Tregs lead to an inflammatory situation, but an increase in their levels can also reduce the inflammatory consequences. Oral administration of the broad-spectrum antibiotics improves Treg production in the lamina propria of the lymphoid tissues as well as in the retina with a decrease in the Th17, Th1, and inflammatory cytokines, ameliorating the severity of the EAU in the mouse models (Nakamura et al. 2016).

All of the above findings indicate that Th17/Tregs imbalance has a pathogenic effect on autoimmune diseases including autoimmune uveitis and the gut microbiome is a potential trigger that should not be ignored.

21.10.3 Destruction of Intestinal Barrier (Increased Intestinal Permeability)

As evidenced earlier, dysbiosis leads to inflammation. This inflammatory process increases the intestinal permeability, as per the Virchow's triad, leading to an intestinal leakage. The leaky intestinal tract becomes an easy escape pathway for the microbiota and their metabolites like lipopolysaccharide (LPS) and β-glucan to the vascular system getting deposited in other tissues like uveal tract or synovial membrane. This entrapment of the molecule into these immune-privileged tissues becomes a pathogenic stimulating inflammatory process causing uveitis or arthritis (Rosenbaum and Asquith 2018). Moreover, morphological changes are noted in the intestinal villi, crypts, and the submucosal layers of the EAU mouse models, with an increased expression of the zonula occludens-1 (ZO-1) and permeability. There is an increased expression of the antimicrobial peptides as well like Reg3γ, S100A8, and lipocalin-2 in the intestinal layers. These morphological changes indicate an inflammatory state (Janowitz et al. 2019). Furthermore, both the degree of Th17/Treg imbalance and the increase in permeability, elevation of lipocalin-2 expression were correlated with the severity of the inflammation in the uveitic and other autoimmune disorders (Leccese and Alpsoy 2019).

21.10.4 Microbial Metabolites

Gut microbiota helps in providing nutrients by breaking the complex carbohydrates into short-chain fatty acids (SFCAs). These SFCAs act as probiotics as well. They are observed to ameliorate inflammation by two mechanisms broadly. SFCAs increase concentration of Tregs in the intestine and the cervical lymph nodes. They also reduce the transportation of effector T-cells from intestine to other sites like spleen. By virtue of these mechanisms, SFCAs are noticed to have an anti-inflammatory action (Nakamura et al. 2017).

Further evidence comes from biochemical studies in patients with AAU and IBD. Feces of AAU patients have an increased expression of unique metabolites as compared to normal controls, like 6-deoxy-D-glucose 1, linoleic acid, N-acetyl-beta-D-mannosamine 3, shikimic acid, azelaic acid, isomaltose 1, and palmitoleic acid (Huang et al. 2018; Maes et al. 2013; Ueda et al. 2008). Though the exact roles of these metabolic phenotypes are not yet fully discovered, metabolic factors in the autoimmune uveitis cannot be overlooked. These observations were extrapolated to further experiments for any therapeutic role as well in uveitis patients. SFCAs supplementation has shown a reduction in the severity of uveitis in EAU mouse models (Nakamura et al. 2017).

It is worth noting that these theories or hypotheses are not mutually exclusive, but explain the pathogenesis of autoimmune uveitis induced by gut microbiome dysbiosis from different aspects. On the one hand, dysbiosis results in the destruction of intestinal immune homeostasis, the emergence of immune disorders due to decreased immune threshold, and the reduced production of anti-inflammatory metabolites, and the increase in intestinal permeability leads to the translocation of microbiota and microbial metabolites from the intestine into the vascular system. On the other hand, microorganisms could induce uveitis indirectly by the activation of retinal specific T-cells through antigenic mimicry, or the microbial metabolites may act directly on the eyes to stimulate the development of inflammation. In addition, it has been proposed that extensive and broad extraintestinal migration of immune cells existed. The trafficking of lymphocytes and inflammatory cells from the gut to the eye has been reported in the EAU mice model, where the gut derived cells related to the severity of EAU were detected in the eye. This may be an essential pathogenic mechanism of uveitis, but it still needs to be determined by further studies.

21.11 All the Way from the Gut to the Retina

All the evidence of activation of autoreactive T-cells in the intestinal microbiota and thereafter migration to the retinal cells needs to be established. Many researchers have looked into the migratory pathway of these autoreactive T-cells passing through the gut towards the eye using transgenic mice expressing photo-convertible fluorescent protein known as the Kaede protein. This special protein changes its color from green to red following violet (405 nm) light exposure. This property of irreversible color change has been used for the study of any transfer or migration of these proteins from one tissue to another (Tomura et al. 2008). Photo-conversion of Kaede protein in the colonic lymphocytes of the experimental mice was performed and presence of any Kaede-positive cells was observed in the retinal tissue. Flow cytometric analysis detected a few Kaede-stained leukocytes in the retina. However, this needs to be properly validated as not only the local intestinal leukocytes pass through the gut, various other cells also pass through the highly vascular intestine. Addition to this, the retina is also a highly vascular structure requiring heavy perfusion of the retinal vasculature for any cell to pass through and enter the retinal tissues. Therefore, a heavy load of T-cells needs to be activated so as to enter the retinal cells to trigger the autoimmune inflammatory process (Nakamura et al. 2017). The concept of an immune-driven gut-retina axis is actively being explored and existing data in animals and in humans raise the scepter of therapeutic approaches that might become possible through targeted manipulation of the microbiome.

21.12 Current Management Options

No standardized protocol has yet been established for patients with AIR. Because of the rarity of the disease, the actual disease course and the response to the available therapeutic option are still unveiled and remain to be determined. Current management options are systemic immunosuppression with corticosteroids, immunomodulatory therapies like azathioprine, methotrexate, intravenous immunoglobulin, biologic agents, and plasmapheresis. The basic mechanism for all the above therapeutic models is either suppression of the innate and the adaptive immune system or to exchange the plasma of the patient with plasma of a healthy individual altogether (Patnaik et al. 2020). They, however, also have various antimicrobial actions (Table 21.1).

As said above the current therapies available for AIR are mainly immunosuppressive and immunomodulatory drugs like corticosteroids, methotrexate, and azathioprine. However, these agents have various other ocular as well as systemic adverse effects like secondary ocular hypertension, osteoporosis, liver, and renal dysfunctions (McEwen et al. 1997). To counteract these side effects, more specific protein-based drugs have been evaluated in various autoimmune inflammatory disorders. Though this new generation of therapies has reduced immunosuppressive adverse effects, they are not devoid of toxicities like cardiac or neurological complications (Hansel et al. 2010). A search for an ideal therapeutic drug, both in terms of efficacy and safety, is still ongoing.

Table 21.1 Antimicrobial action of various immunomodulatory agents

Immunosuppressive agent	Susceptible bacteria	Susceptible fungi	Susceptible viruses
Azathioprine	*Mycobacterium avium paratuberculosis*, *Mycobacterium phlei*, *Escherichia coli*	None	Cytomegalovirus
Methotrexate	*Staphylococcus aureus (also methicillin-resistant strain)*	*Candida albicans*, *Aspergillus* spp.	Cytomegalovirus, Zika virus
Mycophenolate mofetil	*Staphylococcus aureus*	*Candida albicans*, *Candida tropicalis*, *Aspergillus* spp., *Cryptococcus neoformans, Pneumocystis jiroveci*	Herpes simplex virus, measles, Newcastle virus, influenza, hepatitis C, dengue, West Nile virus
Cyclosporine	None	*Candida albicans*, *Aspergillus* spp., *Cryptococcus neoformans*	Hepatitis C, influenza, corona virus, human immunodeficiency viruses

Methionine aminopeptidase 2 (MetAP2) inhibitor is a regulating enzyme for cellular protein synthesis and is primarily involved in the angiogenesis process (Griffith et al. 1998). It is expressed on the proliferating endothelial cells and promotes protein synthesis during endothelial cell proliferation. Inhibition of this enzyme causes p53 activation and induction of the cyclin-dependent kinase inhibitor p21 (CIP/WAF), leading to cell cycle arrest. Apart from the endothelial cells, the enzyme has also been found on the T-cells (Griffith et al. 1998; Mauriz et al. 2007; Zhang et al. 2000).

Lodamine is a polymeric molecule found to inhibit MetAP2 irreversibly (Benny et al. 2008). It suppresses T-cell receptors (TCRs), T-cell proliferation and differentiation leading to reduced production of Th1 and Th17 pro-inflammatory cells. A comparable dose of lodamine to the anti-angiogenic purpose in cancerogenic conditions has been applied in EAU mouse models to evaluate its probable role in treating autoimmune retinopathy (Benny et al. 2008, 2010). It has been shown to have significantly reduced the inflammatory cell infiltration and granuloma formation via normalization of IFN-γ and IL-17 and increased expression of L-selectin CD62L in the lymphoid tissue. CD62L upon exposure to any antigenic stimulus prevents migration of effector T-cells to the sites of inflammation; thereby reducing T-cell activation. Additionally, no collateral adverse effects are seen over the normal immunity and systemic side effects like weight loss or any behavioral changes are usually not seen at the therapeutic dosage (Benny et al. 2008). In addition to the above experimental observations, the drug can be used through oral administration. Since the mechanism of action is different from the current immunosuppressive agents or biologic agents available, it can be used as an adjuvant as well. Larger clinical trials are necessary to evaluate the possible efficiency and safety of each therapeutic approach proposed for future specific intervention.

21.13 Future Therapeutic Considerations

Considering a pivotal role of gut microbiota in autoimmune uveitis , four main therapeutic approaches are developed. This includes antibiotics, probiotics, dietary modifications, and FMT. All these experimental research are useful, if applied for clinical therapeutics. Various approaches have been postulated and tested over the time.

21.13.1 Dietary Modifications

Dietary modifications form the primary intervention measure to stimulate proliferation of beneficial microorganisms. The metabolites by the stimulated bacteria promote immune homeostasis, reduce complement activation, and increase useful metabolic by-products like carotenoids. These improved milieu and the metabolites protect against any damage to the photoreceptors. A high fiber diet improves the gut ecology, thereby enhancing the ability of commensal microbiota of generating

endogenous SCFAs. This dietary modification increases colonization of the commensal microbes; another approach was put forth for targeting specific causative microbial organisms for a specific beneficial effect. Okai et al. (2016) have demonstrated beneficial effects of specific immunoglobulins, targeting certain bacterial strains, in mice models with colitis (Miserocchi et al. 2013).

21.13.2 Prebiotics and Probiotics

Prebiotics are non-digestible food materials that modulate the gut commensals and their interactions influencing the course of the ocular inflammation (Slavin 2013). The prebiotics help to remodulate the gut immune system and the barrier function via becoming metabolic substrates for *Lactobacillus* and *Bifidobacterium* spp. Probiotics, however, are live components of the microorganisms. They further restructure the gut immunity. Response to the prebiotics is highly influenced by the composition of the gut microbiome. Individuals with a *Prevotella*-dominant microbiota can ferment carbohydrates more rapidly than those with a *Bacteroides*-dominant microbiome (Riviere et al. 2016; Flint et al. 2017). The SCFAs which are produced due to probiotics action on prebiotics can diminish the severity of uveitis through enhancing Tregs in the colon and cervical lymph nodes and by a reduced trafficking of the effector T-cells between intestine and spleen (Nakamura et al. 2017). This property of SCFAs and other bacteria-derived fermented dietary metabolites might have a therapeutic effect as well. Exogenous supplementation of these Treg-inducing metabolites needs to be explored further for any such benefits.

Probiotic approach, through administration of live bacterial strains, promotes immune homeostasis milieu via Treg differentiation. This specifically targets the intestinal microbiota. Great potential has been demonstrated experimentally. However, oral administration of the formulation is quite difficult (Ochoa-Reparaz et al. 2010, 2018). Moreover, the utility of probiotic eye drops, containing beneficial microbial agents like *S. boulardii* and *L. rhamnosus* has shown statistically significant improvement in the vernal keratoconjunctivitis group of patients with regard to their itching, burning sensation, and tearing. A downregulation of TLR4 has been observed 4 weeks post-treatment (Watters et al. 2017). Moreover, enteral administration of a microbial component promotes the proliferation of the specific beneficial microorganisms by enhancing the Tregs differentiation affecting the immune homeostasis (Lin 2019).

Most commonly applied probiotics in the experimental mouse model is IRT-5, which contains five probiotics, namely *L. casei, L. acidophilus, L. reuteri, B. bifidum,* and *Streptococcus thermophilus* (Kim et al. 2017). Administration of antibiotics helps in depleting the gut microbiome for a short time and subsequent administration of probiotics helps in recolonizing the intestine with altered beneficial microbiome phenotype. However, it still remains to be solved as to how to increase the colonization of probiotics in the intestine for the maximum therapeutic response.

21.13.3 Antibiotics

Formulation of antibiotics targeting specific bacteria or immunoglobulin or through live bacterial strain administration has been explored but still is in preclinical studies only (De Paiva et al. 2016; Kugadas and Gadjeva 2016; Zaheer et al. 2018). Institution of broad-spectrum antibiotics a week prior to the immunization in EAU model has shown a protective role against the development of severe uveitis, even as compared to that generated in the GF-mouse models (Heissigerova et al. 2016). They act by altering the gut microbiome raising the Tregs and decreasing the Th1, Th17, and inflammatory cytokine levels in the intestinal lamina cribrosa and extraintestinal lymph nodes (Nakamura et al. 2016).

21.13.4 FMT

Fecal microbiota transplant (FMT) is a surgical approach for supplanting an entire intestinal microbiota with a normal community. This has shown curative effects in the antibiotic-resistant Clostridium difficile colitis in large clinical trials (Gough et al. 2011). However, it has its own limitations of being a surgical procedure and lack of proper knowledge of the donor material, its characteristics and regulatory factors. The replacement of the entire gut microbiome of the affected individual with that of a healthy donor, FMT has the potential to improve the intestinal immune ecosystem (Cheng et al. 2019; Choi et al. 2018). Although a fascinating possible approach, many aspects still need further exploration. Along with the transplantation-related issues, there is varied diversity in the gut microbiome in each individual. It is still to be determined which gut microbiome composition would be beneficial for which specific inflammatory condition (Lin 2018).

21.13.5 Cytokines

AIR is provoked by activated $CD4^+$ T-cells. This activated $CD4^+$ T-cell differentiates into effector T-cells, mainly Th1, Th2, and Th17, involved in releasing pro-inflammatory cytokines damaging retina. However, the exact underlying triggering stimulus or factor for activating the autoimmune inflammatory pathway still needs to be unveiled.

The key process in the progression of the autoimmune retinopathy is the transformative nature and plasticity of the T-cell differentiation. Depending upon stimulation of various cytokines, different groups of effector T-cells are differentiated from the activated naive $CD4^+$ T-cells. If interleukin-12 (IL-12) is stimulated, the naive $CD4^+$ T-cells are activated to differentiate into Th1 cells. Similarly, Th2 groups of cells are generated upon IL-4 stimulation. These groups of Th cells contribute to the cellular immune reaction in the ocular structures as well as are found to activate the humoral immune responses as well. Th17 effector cells play a pivotal role in the genesis of AIR. They produce the pro-inflammatory cytokine

IL-17 which recruits monocytes to the inflammatory site inducing neutrophil chemotaxis and stimulates the release of other cytokines (Bettelli et al. 2007). The autoantigenicity of Th17 cells has been shown in the EAU models (Amadi-Obi et al. 2007). Th17 cells and IL-17A have been found to be increased in patients with multiple sclerosis and under intraocular inflammatory conditions (Amadi-Obi et al. 2007; Bettelli et al. 2007; Chi et al. 2008). These observations led to a possibility of utilizing these cytokines for therapeutic purposes.

21.14 Conclusion

AIR is a complex undetermined autoimmune inflammatory ocular condition. It has a varied clinical course as well due to the heterogeneity of the expression of ARA. Role of innate and adaptive immunity in the pathogenesis has been implied. Gut microbiota are at the cross-roads of genetic and environmental factors that can promote ocular conditions such as non-infectious uveitis and age-related macular degeneration, partially via its dynamic influence on mucosal and systemic immunity. They regulate the cross-reactivity with the sequestered retinal antigens through various ways, thereby provoking the autoimmune process. The intestinal microbiome thus represents a salient potential target for therapeutic modulation to treat these potentially blinding conditions. Prospective studies are required to analyze the proposed experimental therapeutic approaches for a clinical implication.

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Part VII

Microorganisms in Pathogenesis and Management of Autoimmune Diabetes

Microorganisms in the Pathogenesis and Management of Type 1 Diabetes (T1D)

22

Muhammad Akram, Tehreem Riaz, Walaa Fikry Elbossaty, Sadia Zafar, Naveed Munir, and Muhammad Muddasar Saeed

Abstract

Diabetes mellitus is considered as a major global health burden particularly for elderly people but now the prevalence is also increasing in the young population. Type 1 diabetes (T1D) is considered as an autoimmune disease resulting from the destruction of β-cell of pancreas from T-cell mediated response and incidences of T1D have been increased both in developed and developing countries. Although the exact mechanism for the development of T1D is still not completely understood, several factors are involved in the pathogenesis of T1D including genetic factors, environmental factors, diet habits, and changes in gut microbiota. From numerous studies it has been revealed that gut microbiota may involve in the pathogenesis of T1D and it is demonstrated that changes in gut bacteria result in insulin dysfunction and cause diabetes mellitus. Moreover, it was predicted that the major link between the alteration of gut microbiome and development of T1D is the destruction of pancreatic β-cells due to autoimmune response evoked through intestinal immunosuppression and the changes in permeability of GIT. The current review was compiled to summarize major mechanism for the

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pathogenesis of T1D development due to microorganism and the possible targets for the management and/or prevention of T1D.

Keywords

Type 1 diabetes (T1D) · Autoimmune disorders · Gut microorganisms · Pancreatic β-cells · Pathogenesis

22.1 Introduction

Recently, diabetes mellitus is becoming a major metabolic disorder with multiple life-threatening complications all over the world. Diabetes mellitus is majorly classified into two types: T1D and type 2 diabetes mellitus. T1D is a multifactorial metabolic autoimmune disease resulting due to genetic as well as environmental factors to destroy the insulin producing pancreatic beta islet cells (β-cells) and common in early age in children and is known as a disease of adolescence. Patients suffering with T1D have insufficient or lack endogenous insulin and required exogenous insulin for proper metabolic functioning throughout the life (Goyal and Jialal 2020). This type of diabetes occurs mostly in genetically susceptible people to environmental changes, and it was reported that the incident of T1D in the many developed countries increased after World War II. The onset of T1D is characterized by polydipsia, polyphagia, polyuria, weight loss, fatigue, and hunger. According to the estimation of International Diabetes Federation, the prevalence of diabetes for the year 2019 was estimated as 4.7–12.2% (19.4–162.6 million people), and expected this rate will rise to 5.1–13.3% (28.6–196.5 million) by 2030 and will reach 5.2–13.9% (47.1–212.2 million) by 2045. 10.8% is higher compared to the countryside (7.2%), and in areas with a high standard of living (10.4%) compared to other low-income areas (4.0%). Today, with the development of science and research fields, it has been found that limitations during the balance of the intestinal microbiota have contributed to the occurrence of many pathological diseases, including T1D (Table 22.1; Fig. 22.1) (Saeedi et al. 2019).

Type 1 diabetes is an autoimmune disease in which antibodies attack pancreatic cells responsible for producing insulin. The digestive system contains many billions of organisms that play an important role in T1D. In terms of epidemiology, the incidence of T1D increases at a rate of 3–5% annually. There are many factors that affect the disease, including environmental and genetic factors. Although women are more susceptible to immune diseases compared to men; however, for T1D, the chances of infection are equal between the two sexes (Mäkimattila et al. 2020). Intestinal epithelium is considered as nature habitat of microorganisms. Animals and Human beings have a large community of microorganisms including bacteria, fungi, archaea, and virus in their gut. From recent studies, microorganisms present in gastrointestinal mucosa are recognized as major environmental factor contributing to the pathogenesis of T1D development. Gut microbiota is also known as “hidden

Table 22.1 Prevalence and expected increases in type1 diabetes in different developed and developing world for 2019, 2030, and 2045

Region	2019—Number of people with diabetes (million)	2019—World-age standardized diabetes prevalence (%)	2030—Number of people with diabetes (million)	2030—World-age standardized diabetes prevalence (%)	2045—Number of people with diabetes (million)	2045—World-age standardized diabetes prevalence (%)
Middle East and North Africa	54.8	12.2	76.0	13.3	107.6	13.9
Western Pacific	162.6	11.4	196.5	12.4	212.2	12.8
South-East Asia	87.6	11.3	115.1	12.2	152.8	12.6
North America and Caribbean	47.6	11.1	56.0	12.3	63.2	13
Europe	59.3	6.3	66.0	7.3	68.1	7.8
Africa	19.4	4.7	28.6	5.1	47.1	5.2

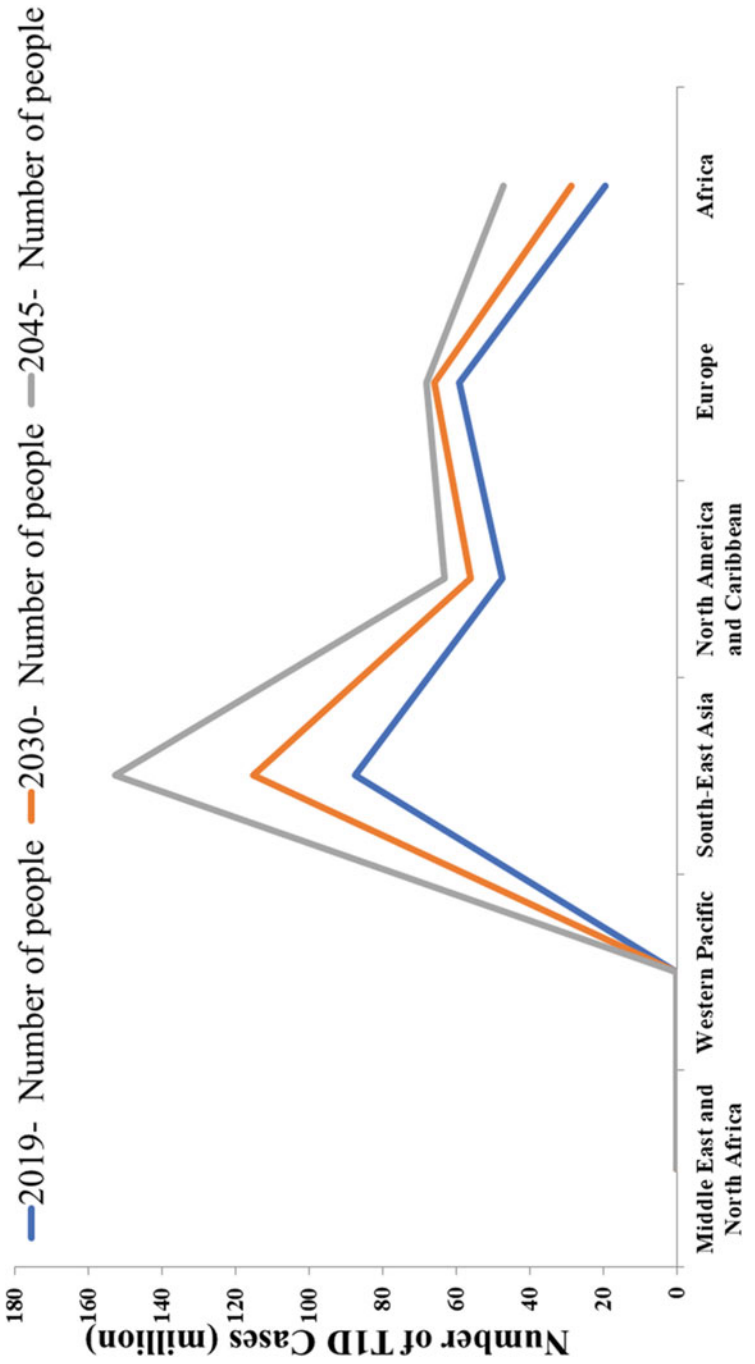

Fig. 22.1 Graphical representation of the prevalence and expected increases in type 1 diabetes in different developed and developing world for 2019, 2030, and 2045

organ" and majorly divided into four phyla which are *Bacteroidetes*, *Firmicutes, Proteobacteria,* and *Actinobacteria* (Matijašić et al. 2020).

Intestinal microorganisms play important role in energy production, to fight against pathogens, maintaining the integrity of intestinal tract, regulation of immunological processes, and maintain the homeostasis (Wang et al. 2019). But at the other hand, alteration and changes in composition of this microbiota known as "dysbiosis" which result in diseases pathogenesis and breakdown of homeostasis (Zheng et al. 2020). Increasing number of evidences suggested that gut dysbiosis, gut leakiness, and gut dysbiosis mediated immunological dysregulation involve in the pathogenesis of T1D mellitus. It is under process to determine that these gut changes have causal or responsive role in type 1diabetes. Once this role will be determined their would-be strategies to prevent the T1D. Current chapter briefly elaborated the alteration and changes in the composition of intestinal microorganism associated with the pathogenesis, prevention, and management of T1D. In addition, this chapter also documented the mechanism through which dysbiosis involves in the progression of T1D.

22.2 Gut Microorganisms and Metabolic Profile

In these days, to evaluate the metabolic profile one of the best methods is to analyze the gut microorganisms' profile and to compare the changes between both of these profiles. Synergistic activities of host and microorganism present in host reflect the best picture of metabolism at systematic level (Zhu et al. 2020). The gut microbiota contains approximately 500–1000 types of bacteria and 100 trillion bacteria in the digestive system. The gut microbiome is called commensal bacteria, and it is divided into Gram positive and Gram negative bacteria. Bacteroidetes and Firmicutes are major (90%), while Actinobacteria and Proteobacteria are less abundant (Cunha et al. 2020).

22.3 Gut Microorganisms and Type 1 Diabetes

Microorganism plays important role in maintaining the metabolism and homeostasis of their host but at the same time these alterations in the microorganisms implicated in the pathogenesis of various diseases such as diabetes mellitus, renal problems, obesity, intestinal problems, atherosclerosis, colorectal cancer, and inflammatory bowel syndrome (Kasprzak-Drozd et al. 2021). From past 50 years, prevalence of infectious diseases has been decreased with the use of vaccinations but some type of bacteria shows resistant to vaccinations and results alteration in their composition (Kamareddine et al. 2020). Dysbiosis has direct impact on the permeability of gut and activates the inflammatory mediators which leads to the destruction of β-cells (Lobionda et al. 2019).

The result of various clinical studies indicated the involvement of gastrointestinal viruses in the onset of T1D. The stool sample and islet autoimmunity from 19 cases

children were analyzed in first report by using next generation sequencing. The detected human viruses were further analyzed by real time PCR (Vehik et al. 2019). In second report both intestinal bacteria and viruses were found to involve in the pathogenesis of T1D. In another study comprising of 11 children showed the presence of Kobuvirus, Human Enterovirus, Parechovirus, Rotavirus, and Parvovirus but there was no association found with autoimmune antibodies. Result of study revealed direct involvement of intestinal viruses in the pathogenesis of T1D (Hober et al. 2013). Intestinal mycobiota is an important microbiota of human beings and alteration or changes in this mycobiota associated with the development of diseases. Various Fungi has been identified in human microbiota and it was stated that it comprises the 0.1% of gut microorganisms (Wu et al. 2021). The most common species of mycobiota detected in gut of human beings are belonging to genera as *Trichosporon*, *Debaryomyces*, *Galactomyces*, *Cladosporium*, *Malassezia*, *Cryptococcus*, *Aspergillus*, *Penicillium, Saccharomyces,* and *Candida*. The species of fungi involved in the pathogenesis of T1D are *Candida species* and *Saccharomyces cerevisiae*. It has been stated from several studies that fungal over growth due to poor glycemic index has been reported and it was concluded that diabetes mostly associated with chronic fungal infection (Chin et al. 2020).

According to most recent study consisting of 16 diabetic children conducted in Spain bacterial genes participating in energy production and in the maintenance of gut integrity were variated in number as compared to healthy children. It was reported that the bacteria which were decreased in number are *Lactobacillus* and *Bifidobacterium* and the bacteria increased in diabetic children were *Veillonella, Bacteroides* and *Clostridium* (Łubiech and Twarużek 2020). The result of study was evaluated by denaturing gradient gel electrophoresis and polymerase chain reaction. In another recent study by using 16S rRNA gene sequencing fecal microbiome of healthy children was examined for the detection of autoantibodies against islet. The result of study correlates the positive response of some bacteria in the formation of islet autoantibodies and indicated that dysbiosis is a regulator for the progression of autoantibodies and onset of disease (Durazzo et al. 2019). Bacteroides and other bacteria producing short chain fatty acid are associated positively and lead to islet autoantibodies formation and autoimmunity (Harsch and Konturek 2018).

The gut microbiota is affected by several factors, including the mode of birth, in which the gut microbiota is determined in infants from birth. As studies have shown that these babies, who were having a normal birth, had their intestinal microbiome close to the mother's vaginal microbiome. While infants who were born in C-section, their gut microbiome was close to the surface microbiome of the mother's skin (Liu et al. 2020). After birth, the microbes are affected by several factors, including diet, antibiotics, medications, and the pH of water. Studies have confirmed that foods contain a large amount of carbohydrates and sugars cause diabetes due to an imbalance in the intestinal microbiota. The wrong treatment with antibiotics kills the intestinal germs, which leads to the reduction of the regulatory T cells and then leads to disease events T1D. In recent years, studies have shown that there is a relationship between the intestinal microbiome and the emergence of T1D. The

results indicated that *Bacillus cereus* reduces starch in T1D, and Bacterium *A. muciniphila* protects mice from developing diabetes (Elhag et al. 2021).

22.4 Other Microorganisms and Type 1 Diabetes

As the occurrence of T1D mellitus follow seasonal pattern number of viruses including mumps, rubella and coxsackie involve as etiological factors in the pathogenesis of T1D. These viruses increase the histocompatibility complex, activate the pro-inflammatory cytokines, and destroy islet beta cell of pancreas. These viruses infect the beta cell or by activating the autoreactive T cells destroy beta cell and result in deficiency of insulin (Duan et al. 2020).

22.4.1 Viruses and Type 1 Diabetes

Since 1864 viruses have been involved in the pathogenesis of T1D and first virus involved was mump virus (Siljander et al. 2019). In 1920, the various experimental studies demonstrated that viruses were major etiological factor in the pathogenesis of diabetes mellitus (Adams 1926; Gundersen 1927). After further experimental studies on mice model in next three decades and diagnostic finding were that coxsackie virus was isolated from the die mice with the diagnosis of diabetes, antibodies of coxsackie virus were found and the viral infection have potential to induce diabetes mellitus (Pappenheimer et al. 1951). After that many experimental studies were conducted to investigate the involvement of the viruses in the etiopathogenesis of T1D. The result of studies indicated the involvement of coxsackie B4 and other viruses in the pathogenesis of T1D. With the latest advancement in medical field vaccination for coxsackie B4 was formulated and administered to prevent the risk of T1D associated with the involvement of Coxsackie virus in the etiology of T1D (Hyöty et al. 2018). Studies demonstrated that highly variable nature of viruses is mostly associated with the occurrence of pathological problems.

22.5 The Mechanisms Through Which Gut Microorganisms Influence the Development of Type 1 Diabetes

A large number of studies proposed that gut permeability and immunological dysregulation are two main factors involved in the development of T1D. Disturbed profile of intestinal microorganisms by increasing gut permeability and affecting homeostasis influences the T1D development (Walaa Fikry 2017). Due to the constant ability of intestinal microorganisms to interact with immunological cell, gut microorganisms are considered as important part of immune system. These microorganisms play pivotal role for the establishment, maturation, and tolerance of immune system at early stages of life. In genetically predisposed subjects, dysbiosis results in destruction of insulin producing beta islet cells of pancreas in

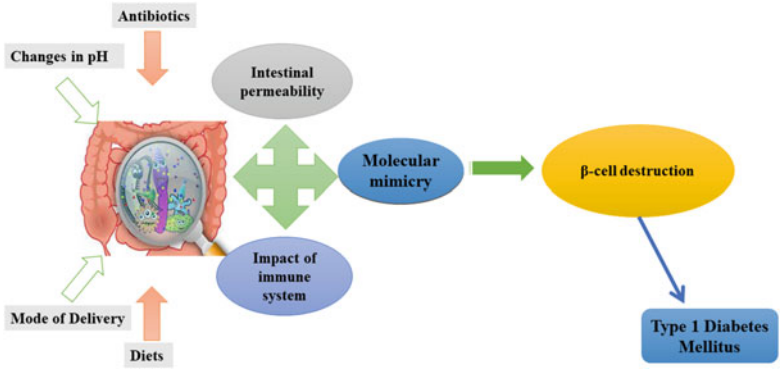

Fig. 22.2 Possible mechanisms involved in the development of T1D due to gut microbial pathophysiology

uneducated communities. Hygiene hypothesis demonstrated that at early stage of life deficiency of microorganism stimulation causes immune-mediated diseases. Hence, it is concluded that intestinal microorganism stimulating immune responses at early childhood is very important to prevent the onset of T1D (Zhou et al. 2020). Although the relationship between the gut microbiome and the establishment of diabetes is a complex process, but following mechanisms involvement are considered (Fig. 22.2).

22.5.1 Intestinal Permeability

Intestinal barrier regulates the permeability of intestinal mucosa in an organized functional unit consisting of many layers comprising of intestinal microorganisms, immune cell, mucus, epithelial cells, and lymphoid tissues. Disruption of this intestinal barrier results in increased permeability of gut (Yoo et al. 2020). The major site of pathogen attack is intestinal mucosa and in case of strong gut integrity it provides first line of defense against pathogen invasion but increased permeability of gut facilitates these pathogens to invade the host cell easily. The intestinal barrier maintains the permeability of the mucosa, when it is disrupted, the permeability of the membrane increases. Studies have confirmed that if there is a penetration of the mucous membrane, this leads to an increase in the stray T cells, which helps in the occurrence of inflammation in insulin secreting cells (Hansson 2020).

Intestinal permeability is also known as leaky gut resulting in dysregulation of immunological response proposed as main causative factor in the pathogenesis of T1D (Paray et al. 2020). Some experimental studies demonstrated that Bacteroides are positively associated in the development of T1D. These bacteria cause fermentation of lactate and glucose to acetate, succinate and propionate which inhibit the synthesis of mucin which is essential to maintain the integrity of gut barrier and results in leaky gut. These bacteria by inhibiting the assembly of Tight Junction (TJ) barrier increasing the permeability of intestinal barrier led to the pathogenesis and

progression of T1D (Chakaroun et al. 2020). Gut permeability investigated by both animal model and by human model studies demonstrated that permeability of barrier or dysfunction of barrier is a main feature of T1D. Some researchers stated that insulitis and hyperglycemia result in increased gut permeability. But at the same time some researchers stated that gut permeability is a cause of T1D not an effect because increased gut permeability has been noticed before the onset of T1D in many experimental studies. According to most cited experimental study conducted by Bosi et al. indicated that leaky gut has been observed before the disease manifestation. Increased gut permeability is a major component in the progression of T1D because leaky guts allow the pathogen invasion which results in infection and stimulation of inflammatory mediators which can destroy the beta cell of pancreas and inhibit the insulin synthesis (Hills et al. 2019).

Butyrate producing bacteria are highly essential because butyrate maintains the integrity of gut and has anti-inflammatory efficacy. But in case of T1D decreased number of butyrate producing bacteria was observed. Onset of T1D can be prevented with increased number of butyrate producing microbiota with their anti-inflammatory and gut integrity maintenance potential. According to most recent studies it was stated that butyrate regulate the mucin production, and in the assembling of tight junctions ultimately having impact on TJ barrier proteins to maintain the integrity of gut barrier. Bacterial species converting lactate to butyrate play remarkable activity to produce mucin, formation of TJ and promote gut health. Another preventive measure of T1D is casein diet administration which also has good impact on integrity of gut barrier (Sorini et al. 2019).

22.5.2 Molecular Mimicry

Bacterial proteins are similar in molecular structure to those in the pancreas, for example, Mgt protein of *Leptotrichia goodfellowii*, which is similar to IGRP protein found on pancreatic cells (Sami et al. 2020). Therefore, activation of immune system against such bacterial proteins might lead to the destruction of pancreatic cells and may play important role in the development of T1D due to autoimmune disorders.

22.5.3 Impact of Immune System

Lymphocytes, especially the macrophage, infiltrate the pancreas during insulitis, where they bind to pancreatic cells, helping to produce $CD4^+$ T cells, which in turn destroy the beta cells responsible for producing insulin. By disturbing the normal functionality of immune system dysbiosis in early life has major impact in the progression of T1D (Mishra et al. 2019).

22.5.3.1 Impact on Innate Immunity

Innate immune system has major contribution in the onset of T1D and studies stated that reaction of immune system with intestinal bacteria leads to progression of T1D.

Toll-like receptors (TLRs) being an important recognizer of pathogen are best players to maintain intestinal homeostasis and activate the innate immunity (Sami et al. 2020). By using TLRs many microorganisms present in gut mucosa can inhibit or facilitate the islet autoimmunity by activating the signaling pathway. The very first effort was designed in MyD88-deficient NOD mice to investigate the role of intestinal microorganism in the progression of type 1 diabetes. MyD88 has potential to recognize the stimulus stimulated by microorganisms and the mice were free from diabetes and NOD receptor can detect the bacterial products and involved in the progression of diabetes (Mishra et al. 2019).

22.5.3.2 Impact on Adaptive Immunity

With the development of adaptive immunity via signaling the immune system health can be protected and achieved. Alteration in composition of intestinal microbiota has negative impact on the development of adaptive immunity at different levels such as natural killer T cells, $CD4^+$ T cells, $CD8^+$ T cells, and invariant T cells (Lee et al. 2020). T helper cells are important and vital component of adaptive immune system and play important role in the mediation and controlling of immune reactions. Disturbed or imbalanced immune reactions lead to the destruction of insulin producing islet beta cells of pancreas (Ferreira et al. 2020). The maturation of T cells is highly essential for the tolerance of immune responses at early life. Th17 when overexpressed or dysregulated led to the pathogenesis of T1D. The normal activity of Th17 is to clean out the pathogens causing infection and to produce interleukin. But in case of increased inflammatory response caused by Th17 lead to autoimmunity which led to the progression of autoimmune diabetes mellitus (Kogut et al. 2020). Altered bacterial composition is the main cause of the activation of $CD8^+$ T cells which have destructive effect on islet beta cells. According to the findings of recent clinical studies it was indicated that $CD8^+$ T cells were found activated in altered bacterial composition in intestinal mucosa leading to pathogenesis of T1D (Dutta and Lim 2020).

22.6 Management Possibilities for Type 1 Diabetes Prevention

The intestinal microbiota may be used in the early diagnosis of T1D, as the occurrence of any defect in the microbiome is evidence of the emergence of T1D, and the increase in Bacteroidetes is an indication of the onset of T1D. In addition to predicting diabetes, the gut microbiome may be used to treat T1D, as eating a probiotic which might prevent the development of diabetes (Sorini et al. 2019). Some species of microorganisms result in the onset of many autoimmune diseases, but there are some species of microorganism which play healthy role in the prevention of such diseases. Experimental studies revealed that manipulation of gut microorganisms acts as preventive microbial therapy in the prevention of T1D in people at genetic risk. Nowadays, gut microbiota is highly remodeled at early childhood and puberty. These remodel microorganism culturing in suitable conditions and environment to prevent the progression of T1D and other

autoimmune diseases. In an experimental study gluten free chow feeding mice show significant reduction in hyperglycemia and provide support to the idea that feeding control environmental conditioned remodeled microorganism having therapeutic potential in the management of various ailments (Ma et al. 2020). Culturing of butyrate producing bacteria plays helpful role in the management of T1D. Parasitic helminths having immunomodulatory activity provides protective effect in the prevention of autoimmune diseases. Increased diversity of bacterial species converting lactate to mucin is another beneficial and healthy step in the management of T1D. Strategies for the regulation of new frame work are required to provide therapeutic results with the use of microorganisms (Elsherbiny et al. 2020).

22.7 Diabetes and Dysbiosis: A Causal or Contemporary Phenomenon

It was reported during clinical and experimental studies that dysbiosis contributes in the pathogenesis and progression of T1D mellitus. Alteration in composition of microorganism leads to the progression of T1D by two steps (Mangalam et al. 2021). In first step, dysbiosis start at early life cause type 1 and autoantibodies formation. In second step, reduced biodiversity of healthy microbiota, increased diversity of unhealthy microorganisms, and increased inflammatory reactions lead to the progression of T1D. It is a challenging phenomenon to find out that this relationship is contemporary or causal. More studies should be required to find out this phenomenon so that prevention and management could be done easily.

22.8 Conclusion

A large number of evidences from clinical and experimental studies revealed that changes in the microbial flora lead to the autoimmune microbiome over time, particularly on comparing with healthy microbiomes dysbiosis or alteration in the composition of intestinal microorganisms including reduced or increased diversity of microorganisms contributes largely in the development and progression of T1D mellitus. The major pathophysiological mechanisms through which microorganisms cause T1D reported included the increased gut permeability and dysregulation of immune system modulating the intermediates like lactate and glucose to succinate, acetate and propionate required for healthy intestine. In addition, to intestinal microorganisms some virus having seasonal impacts lead to the progression of diabetes mellitus. Proper regulation of adaptive and innate immunity via the regulation of immune system and gut integrity progression of T1D can be prevented. Butyrate producing bacteria and bacterial species converting lactate to mucin play important role in maintenance of gut integrity and proper regulation of immune responses used in the management of T1D.

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Part VIII

Current Challenges and Future Prospects in Research Towards Microbial Pathomechanisms and Therapeutic Aspects of Autoimmune Diseases

The Influence of the Microbiome and Genetic Associations on Immune Functions and on Autoimmune and Autoinflammatory Diseases

23

José Moreno and César Pacheco-Tena

Abstract

Autoimmune and autoinflammatory diseases are different ends of several common genetic traits and pathways ending in chronic inflammation, which depends on adaptive and innate immunity, respectively. Autoimmune but not autoinflammatory diseases are strongly associated with major histocompatibility class II alleles, which define the target antigen for T and/or antibody-dependent tissue damage. Both types of diseases can be triggered and maintained by internal or external factors. Among the latter, dysbiosis of the microbiota, which profoundly influences the nature of the immune-mediated inflammation and immune tolerance, has received a great deal of interest over the past two decades. Here we discuss the recent advances in the knowledge of the immune system and the mechanisms leading to autoimmunity or autoinflammation. Moreover, we revise some of the most recent information about the possible roles of the microbiota on these processes.

Keywords

Autoimmune diseases · Genetic associations · Microbiota · Immunity · Immune tolerance · Autoinflammatory diseases

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23.1 Introduction

The germ theory of disease became a reality in the late nineteenth century. However, the limited knowledge at the time led to the identification of only a few infectious diseases. Much farther were the medical and scientific communities to imagine the great variety of microorganisms existing, and that many of them not only were harmless, but that their interaction with the host was essential for life. What we now know as microbiota refers to the sum of microorganisms living within an organism, with microbiome also including the products of such microorganisms and their interactions with the host microbiome (de Vos et al. 2022). Although these interactions occur essentially in epithelia, their impact goes deep into practically all tissues of the body.

Non-pathogenic microorganisms living in a major organism have been traditionally classified into symbionts and pathobionts (de Vos et al. 2022). While symbionts are of major importance in normal physiology, pathobionts, defined as microorganisms that can cause harm only under certain circumstances, may persist for long periods without ill effects, until, at a given time point, they turn pathogenic and cause disease in a previously unaffected individual (Butler and Gibbs 2020). A previously "harmless" bacteria can turn pathogenic under several circumstances, such as changes in the overall composition of the microbiota that can be triggered by broad-spectrum antibiotics, geographical relocation, debilitating diseases, and immunocompromise (Butler and Gibbs 2020). Pathobionts can cause disease only in people of certain genetic backgrounds (Sanna et al. 2022). Without a clear definition of what is a pathobiont, many times this term is used for disease-associated microbes without proof of causality. As recently pointed out, there is no clear boundary between what is classified as a symbiont and a pathobiont (Jochum and Stecher 2020). Because of this, we refer to the pathogenic potential (PP) of particular members of the microbiota (Jochum and Stecher 2020), which is variable depending on the presence or other microorganisms or the genetic characteristics of the host. Finally, pathogens are the cause of specific infectious diseases and will not be considered here unless in cases with solid evidence of specific association with autoimmune or autoinflammatory diseases. Changes in the composition of what is considered a normal microbiota are known as "dysbiosis." Because the intestinal microbiota is, by far, the most abundant and there is evidence of its role in processes that go from glucose tolerance, obesity, autoimmune diseases, inflammatory bowel diseases (IBDs), osteoporosis, and many others (Rosen and Palm 2017); most of the data herein refer to the gut microbiome.

23.2 Autoimmunity and Autoinflammation

Before we get into the associations of microorganisms to autoimmunity, it is important to define what we call an autoimmune disease, and how we distinguish them from autoinflammatory diseases. Although such distinction could be subtle and may be even of little practical relevance, it is important in terms of classification and

understanding of their pathogenesis. The website for the American Autoimmune Related Diseases Association (AARDA, https://autoimmune.org/disease-information/) lists over 100 diseases as being autoimmune. However, some of them are repeated more than once under different names, they include autoinflammatory or even infectious diseases and, finally, others do not fulfill criteria for true primary autoimmune-mediated damage. We define an autoimmune disease as a chronic inflammatory pathological condition resulting from the direct or indirect action of adaptive immunity. Either antibodies or T cells ($CD4^+$ or $CD8^+$) specifically directed against a self-antigen, and a strong association with major histocompatibility complex (MHC) class II susceptibility alleles. Table 23.1 shows a non-exhaustive list of diseases that fulfill these criteria. Although we identified 42 diseases as such, we consider here only 32 with sufficient information for analysis. Conversely, autoinflammatory diseases arise from the action of innate immunity with or without the secondary participation of adaptive immunity with a weak or no association with MHC class II susceptibility alleles. Many autoinflammatory diseases are monogenic with a Mendelian inheritance, whereas a few others are complex diseases, of which we have considered here only 13 (Table 23.2). Common features include the absence of a specific infectious agent or exogenous trigger in the affected tissue or organ.

Autoimmune and autoinflammatory diseases have many, highly variable, gene associations, many of which are shared between them (Dai et al. 2019; Gonzalez-Serna et al. 2020; Mirza et al. 2014; Osgood and Knight 2018; Ye et al. 2018; Zhang et al. 2020). Moreover, these diseases are polygenic, and their phenotypic features are also variable and strongly influenced by external factors and by non-immune endogenous factors (Goodnow 2007; Langan et al. 2020; Steinman 1995). Here, we focus primarily on complex-polygenic autoimmune and autoinflammatory diseases because of their shared features, including the role of exogenous agents and their common gene associations, suggesting common pathogenic pathways, regardless of the differences in their dependence or not of the adaptive immune system.

Two autoimmune diseases: autoimmune polyendocrine syndrome type 1 (APS-1) or autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) (Gibson et al. 1998; Peterson et al. 1998) and IPEX (Bennett et al. 2001) are monogenic. APS-1 is a recessive-autosomal disorder due to defects in the gene that codes for the autoimmune regulator protein (AIRE), and IPEX is a X-linked disorder, consequence of a defective *FOXP3* gene that encodes a transcriptional regulator that controls the differentiation of regulatory T cells (Treg), a major and essential component of self-tolerance, which is necessary to prevent autoimmunity (Fontenot et al. 2003; Sakaguchi et al. 2001). Monogenic lupus (Belot and Cimaz 2012) is a variant of systemic lupus erythematosus (SLE) due to mostly monogenic defects in genes coding for several, mainly scavenger, proteins. In the case of autoinflammatory diseases, many of them, not discused here, are monogenic and their number is continuously growing.

Table 23.1 List of complex autoimmune diseases

Complex autoimmune diseases
1. Hashimoto's thyroiditis
2. Graves' disease
3. Addison's disease
4. Type 1 diabetes
5. Pernicious anemia
6. Pemphigus vulgaris
7. Pemphigus foliaceous
8. Bullous pemphigoid
9. Fogo salvagem
10. Vitiligo
11. Multiple sclerosis
12. Myasthenia gravis
13. Multifocal motor neuropathy
14. Chronic inflammatory demyelinising polyradiculoneuropathy (CIPD)
15. Guillain-Barre syndrome (no demyelinising)
16. Optic neuromyelitis
17. Type I narcolepsy
18. Goodpasture's syndrome
19. Autoimmune encephalitis (probably several different syndromes)
20. Sympathetic ophthalmia
21. Primary biliary cirrhosis
22. Autoimmune hepatitis
23. Celiac disease
24. Rheumatoid arthritis
(a) Seropositive RA
(b) Seronegative RA
25. Juvenile idiopathic arthritis
26. Lupus erythematosus
(a) Systemic lupus erythematosus, including Evans syndrome, ITP, AHA
(b) Subacute cutaneous lupus erythematosus (including discoid lupus and lupus profundus)
27. Primary Sjögren's syndrome
28. Dermatomyositis
29. Juvenile dermatomyositis
30. Scleroderma (systemic sclerosis and localized forms)
31. Undifferentiated connective tissue disease (MCTD, etc.)
32. ANCA-positive systemic vasculitis
(a) Granulomatosis with polyangiitis
(b) Eosinophilic granulomatosis with polyangiitis
(c) Microscopic polyarteritis

Table 23.2 List of complex autoinflammatory diseases

Complex autoinflammatory diseases
1. Psoriasis
2. Inflammatory bowel disease
3. Crohn's disease
4. Ulcerative colitis
5. Ankylosing spondylitis
6. Other seronegative spondyloarthritis (reactive arthritis)
7. Sarcoidosis
8. Juvenile idiopathic arthritis (systemic, Still's disease)
9. Adult Still's disease
10. Vitiligo
11. Takayasu's arteritis
12. Giant cell arteritis and polymyalgia rheumatica
13. ANCA-negative arteritis

23.2.1 Some Immunological Facts to Consider

We currently accept that the vertebrate immune system possesses at least two major branches: innate and adaptive immunity (Janeway and Medzhitov 1998), of which the second is characterized by immunological memory (see below). Their distinction matters not only to justify the differences between autoimmune and autoinflammatory diseases, as it is also necessary to understand the involvement of the microbiota in the pathogenesis of these diseases.

Innate immunity is present in all multicellular organisms and precedes infection (Janeway and Medzhitov 1998). Its receptors such as PRRs (pattern recognition receptors) recognize molecular patterns characteristic of phylogenetically distant organisms (Janeway and Medzhitov 2002), are expressed by their effector cells, and become activated upon contact with pathogen-associated molecular patterns (PAMP), which differ widely between living beings from different kingdoms or phyla. Moreover, innate immunity reacts with damage-associated molecular patterns (DAMPs) (Chen et al. 2015; Edye et al. 2013), which derive from tissue debris that do not normally circulate freely. Innate immunity has no dedicated organs, its cells arise in the bone marrow, its effector mechanisms are not specific, and it is present in all tissues of the organism (Akira et al. 2006; Liu 2001). Cells of innate immunity include polymorphonuclear leukocytes (PMNs), mononuclear phagocytes (including dendritic cells), mast cells and innate lymphoid cells (ILCs), among others (Galli et al. 2011). Soluble mediators include complement proteins, pentraxins, and antimicrobial peptides.

PRRs include Toll-like receptors, (TLR), NOD-like receptors (NLR), RIG-like receptors (RLR), and C-lectin like receptors (CLR), all of which bind different kinds of PAMP- and DAMP-containing molecules, mostly polysaccharides, nucleic acids, lipo-peptides (Gordon 2002; Strasser et al. 2012). Although the PRR diversity and

specificity are limited, each PRR binds to multiple, structurally related ligands. PRR recognizes PAMP from any microorganism, including pathogens, pathobionts, and commensals. The role of PRR is to alert the host of the invasive presence of a potential threat and to alert the organism to be prepared for a possible intrusion (Matzinger 2002, 2012).

PRR ligands activate signaling pathways that are shared with some inflammatory cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF), and IL-17A, leading to activation of NF-kB transcription factor (Kagan and Barton 2014; Kawai and Akira 2010; Medzhitov and Janeway 2000; Paul 2011). RLR and TLR3 activate interferon regulatory factors (IRFs). NLR activate programmed cell death pathways other than apoptosis known as pyroptosis or necroptosis through complexes called inflammasomes, which activate caspase 1, an enzyme that cleaves the precursor of IL-1β to its active form (Hornung et al. 2009; Mariathasan et al. 2004).

Conversely, adaptive immunity is evolutionarily recent and present only in vertebrates. Their cellular components are T and B lymphocytes, which recognize their ligands specifically as antigens, leading to the establishment of immunological memory as its hallmark. T and B cells bear highly diverse, clonally distributed, receptors that interact specifically with their ligands, which in the presence of co-stimulatory signals induce cell activation and differentiation into effector cells (for T lymphocytes) and antibody-producing cells (for B lymphocytes), and (for both) into memory cells (Paul 2011).

Major subsets of T lymphocytes, with similar antigen receptors (TCR) on their surface, but that differ in their co-receptors, are CD4 and CD8 T cells. The TCR α and β chains only recognize antigens (always proteins) as short peptides bound to highly polymorphic glycoproteins of the MHC on the surface of antigen-presenting cells (APC) (Clatza et al. 2003; Moreno and Lipsky 1986b). MHC molecules are class I (MHCI) that present peptides to $CD8^+$ (cytotoxic) T cells, or class II (MHCII) that present peptides to $CD4^+$ (helper and regulatory) T cells. Helper T (Th) cells differentiate onto functional subpopulations that secrete different sets of cytokines and lead to different forms of inflammation, which are of importance to understand the pathogenesis and treatment of distinct autoimmune conditions.

Peptides bound to either class of MHC molecules arise from intracellular antigen processing by APC (Moreno et al. 1991). A functional consequence of MHC polymorphism is that each MHC allele binds distinct groups of peptides that share residues capable of selectively binding some MHC alleles (Moreno et al. 1990). In addition, due to MHC polymorphism, T cell responses are genetically restricted (Paul 2011). A third, undesirable, consequence is alloreactivity (Moreno and Lipsky 1986a). Finally, it is important to consider that the polymorphism of the MHC and the existence of several multiple MHCI and MHCII alleles confers a given species the advantage of presenting a very large number of peptides from many different proteins and, in this manner, respond against a greater number of pathogens. However, this evolutionary advantage increases the risk of autoimmunity.

As mentioned, to become activated by an antigen, T and B cells must be able to distinguish self from foreign antigens. However, these cells are intrinsically unable to do this distinction as their activation, in addition to specific antigen, depends on

the simultaneous presence of molecules that are naturally identified as foreign (Medzhitov and Janeway 1998, 2002). This is where innate and adaptive branches of immunity interact, as the ligands of the former are recognized by inherited PRR on their APC, particularly dendritic cells (DCs), members of innate immunity that convey signals from PAMPs or DAMPs, now as co-stimulatory signals, to T lymphocytes, which in this manner become activated to initiate an adaptive immune response (Liu 2001; Pulendran and Ahmed 2006). In the case of B cells, co-stimulation is mostly indirect through helper ($CD4^+$) T cells (Th), which are necessary for B cell activation, maturation of the antibody responses, and differentiation onto memory B cells. Th provide B cell help through the release of cytokines and cognate interactions, such as the TNF family protein CD40 ligand that triggers mechanisms necessary for the maturation of the humoral immune response and for the establishment of B cell memory CD40 (Klaus et al. 1994; Spriggs et al. 1993).

A final point to make is that not all T or B cells belong to the adaptive immune system. Some TCR-bearing cells respond to invariant antigens, including non-protein molecules bound to classic or not classic MHC molecules, and do not lead to immunological memory. Similarly, some B cells, such as B1-type and marginal-zone cells produce antibodies that do not need antigenic stimulation, nor they differentiate into memory cells. Although some syndromes, as cold-antibody autoimmune hemolytic anemia, are mediated by these cells, they are not considered here (Harsha Krovi et al. 2020; Margulies 2014; Monteiro and Graca 2014; Spits et al. 2016; Taniguchi et al. 2010; Wencker et al. 2014; Zhu et al. 2016).

23.2.2 Immune Tolerance

Tolerance induction has been thoroughly studied for T cells and hence, protein antigens. With a few exceptions, T cells only respond to peptides (Moreno et al. 1990). On the other hand, although B cells (and antibodies), can recognize practically any type of molecule, the induction of memory, class switch recombination and affinity maturation, require T cell help (Paul 2011). During cognate Th cell–B cell interaction, Th cells recognize any given peptide bound to MHCII on the B cell surface (for protein-specific B cells), whereas the B cell receptor (BCR) binds peripheral epitopes of the protein (Paul et al. 1970). Thus, any Th cell specific for any peptide bound to MHCII on the B cell surface (resulting from intracellular processing of the recognized protein) can provide help. This allows the TNF family molecule CD40L (on the T cell) to interact with its receptor, CD40 (on the B cell) to activate the class switch recombining enzyme AID (Muramatsu et al. 2007), which achieves both somatic hypermutation for affinity maturation of the antibody response and class switch recombination, after which IgM changes to a different immunoglobulin subclass, depending on the local cytokine milieu.

B cells specific for non-protein antigens need their antigen to be bound (covalently or not) to a protein that is the carrier for T cell help (Katz et al. 1970; Paul et al. 1970). These interactions are essential for B cell memory. B cell antigen recognition without T cell help (T-independent responses) does not generate memory. Because

of this, tolerance must be achieved on the T cell side of the immune response and, therefore, antibodies to non-protein antigens can receive help from any T cell, including those directed at foreign proteins (Sakaguchi et al. 2006; Swat et al. 1994; Zuklys et al. 2000). That is why tolerance to non-protein antigens is harder to achieve, which applies mainly for tolerance that depends on T cell clonal deletion because Treg can maintain tolerance in most immunocompetent individuals.

23.2.3 Genetic Susceptibility to Autoimmune and Autoinflammatory Diseases

As mentioned, autoimmune diseases are highly heterogeneous both clinically and genetically (Goodnow 2007). There is a great overlap in the association of gene variants with different autoimmune diseases, as well as between autoimmune and autoinflammatory diseases. Many genetic associations to these diseases correspond to genes related to proteins that belong to inflammatory pathways, such as kinases, protein tyrosine or serine phosphatases, as well as adaptor proteins. Involved pathways include cytokine receptor second messengers, antigen-receptor and co-stimulatory-receptor signaling pathways, etc.

An important fact of genetic associations is that a single gene can be associated with more than one autoimmune, and even autoinflammatory disease, usually in combination with other genetic variants (Ye et al. 2018). Our interpretation of this is that these gene combinations create a status of a lowered threshold for inflammatory responses. In the case of autoinflammatory diseases, innate immune activators would suffice to develop the pathological state and the clinical features. However, autoimmune diseases require activation of self-antigen specific $CD4^+$ T and B cells, and in some diseases, $CD8^+$ T cells (Goodnow 2007). This is when genetic association with MHCII alleles takes relevance, as different alleles of MHCII select particular peptides to present to $CD4^+$ T cells (Moreno et al. 1990), which drives the response to specific antigens in the tissues affected by the different autoimmune diseases (Fiorillo et al. 2017; Gregersen 1989; Kalbus et al. 2001). This explains why most gene associations are not related to a particular disease phenotype, whereas association with MHCII alleles has a much closer approach to specific diseases. Table 23.3 shows some immunologic features of several autoimmune diseases and depicts their most relevant genetic associations.

In contrast to autoimmune diseases that have a high female to male bias, autoinflammatory diseases have similar female to male ratios, suggesting differences in their pathogenesis. There is evidence that adaptive immunity is stronger in females, whereas innate immunity is similar in males and females, further supporting the notion that autoimmune and autoinflammatory diseases are mediated by adaptive and innate immunity, respectively.

Genome wide association studies (GWAS) of complex autoinflammatory diseases have found a strong relation among a group of them, including plaque psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), reactive arthritis, some forms of juvenile chronic arthritis (JCA), inflammatory bowel diseases (IBDs), and

Table 23.3 Features of complex autoimmune diseases

Organ	Disease	Mediators	Target antigens	Major MHCII	Other genes
Endocrine	Hashimoto's thyroiditis Graves' disease	CD4 (Th1, Th17) CD8, AutoAb AutoAb	Thyroglobulin, thyroid peroxidase TSH receptor, thyroglobulin	DRβ1-Arg74 DRB1*1403	**PTPN22**, SLAMF6,**CTLA4**, GPR174, ITM2A **PTPN22**, **FCRL3**, SLAMF6, TRIB2, **CTLA4, CD28**
	Addison's disease	CD4 (Th1, Th17) CD8, AutoAb	Steroid 21-Ohse (21-OH)	DQA1*0501 DQB1*0201 DQA1*0301 DQB1*0302	**PTPN22**
	Type 1 diabetes	CD4 (Th1, Th17) CD8, AutoAb	Insulin, GAD65	DQA1*0501 DQB1*0201 DQA1*0301 DQB1*0302	**PTPN22**, GAD65, insulin
	APS-1 (APACED): Thyroiditis, Addison's, T1D, oophoritis, pernicious anemia, vitiligo	CD4 (Th1, Th17) CD8, AutoAb	IFNω, NALP-5, CaSR, 21-OH, 17αOH, TPO, thyroglobulin, etc.	DQA1*0501/ DQB1*0201 DQA1*0301/ DQB1*0302	**AIRE** (monogenic)
Skin (bullous)	Pemphigus vulgaris Pemphigus foliaceus Bullous pemphigoid Dermatitis herpetiformis	IgG4 AutoAb AutoAb AutoAb IgA immune complexes	Desmoglein 3 Desmoglein 1 Hemidesmosomes BP180, BP230 transglutaminases	DRB1*04:02 DRB1*01-DQB1*05: 01/03 DQA1*05:05 Same as celiac disease	ST18 NOTCH4, STEAP2-AS1
Neurological	Multiple sclerosis	B, CD8, Th1, Th17 Molecular mimicry EBNA1 (EBV)	EBNA1 (EBV) cross reactivity with glial CAM	DRB1*15:01, DRB1*01:01 DQA1*04: 01, DQB1*06:02 DQA1*01:01	AHI1, CD58, CDSN, CLEC16A, COL11A2, DPH5, **FCRL3**, **IL2RA**, IQCB1, MMEL1, NFKBIL1, PSMB8, TMEM39A, TNFRSF1A, **TNFSF14**, DKKL1

(continued)

Table 23.3 (continued)

Organ	Disease	Mediators	Target antigens	Major MHCII	Other genes
	Myasthenia gravis	IgG4 AutoAb	Nicotinic acetyl choline receptor Muscle-specific kinase	DQB1*05:01 (thymoma)	**PTPN22**, TNFRSF11A, **CTLA4**, **TNIP1**, ZBTB10, CHRAN1/D, CHRNB1
	Optic neuromyelitis	AutoAb	Aquaporine-4	DQA1*05:03	
	Type 1 narcolepsy	CD4, AutoAb	Orexin receptor PGD_2 receptor	DQB1*06:02	
	Acute disseminated encephalomyelitis	AutoAb	Myelin oligodendrocyte glycoprotein	DQB1*03:03	
	Encephalitis with psychosis	AutoAb	N-methyl-D-aspartate-receptor	DRB1*16:02	**IRF7**, **BANK1**, TBX21
	Limbic encephalitis	AutoAb	LGI1	DQB1*02: 02/ DQA1*02:01	
Gastrointestinal	Autoimmune gastritis and Pernicious anemia (APS-1)	Th1, Th17, AutoAb	Parietal cell H^+/K^+ proton pump, intrinsic factor	DQA1*0501/ DQB1*0201 DQA1*0301/ DQB1*0302	**AIRE**, **PTPN22**
	Celiac disease	Th1	A-gliadin (not an autoantigen)	DQA1*0501/ DQB1*0201 DQA1*0301/ DQB1*0302	**UBASH3A**, **CD28**, **CSK**
	Goodpasture's syndrome	AutoAb	Collagen IV α3 chain	DRB1*1501	
	Primary biliary cholangitis (cirrhosis)	Th1, Th17, AutoAb	Mitochondria	DRB1*08:01, DRB1*08:03	**FCRL3**, INAVA, PRDM1, **IRF7**, CCR6, **CD226**, **IL12RB1**
	Autoimmune hepatitis	Th1, Th17, AutoAb	Smooth muscle actin	DRB1*0301, DRB1*0401	**CD28**, **CTLA4**, **ICOS**, **AIRE**, SYNPR

Systemic	Rheumatoid arthritis	Th1, Th17, AutoAb	Citrullinated proteins Rheumatoid factor	DRB1*0401 QKRAA 70–74	**PTPN22**, **STAT4**, TRAF1/C5, ICAM1, IL6R, CCL21, **IL2/21**, **CD40**, ICAM3, PADI4
	Sjögren's syndrome	Th1, Th17, AutoAb	Ro/SSA, La/SSB, FR	DRB1*0301	
	Dermatomyositis (adults)	Th1, Th17, AutoAb	tRNA synthetases	DRB1∗03:01, DQB1∗02:01	
	Systemic sclerosis (diffuse) Limited scleroderma	CD4+ T cells, AutoAb CD4+ T cells, AutoAb	Topoisomerase (ATA) RNA polymerase III Centromere	DQA1*05:01 DPA1*02:01/ DQB1*03:01 DRB1*11:04 DQA1*02:01 DRB1*08:01, DRB1*07:01	**TNFSF4**, **IRF5**, IRF8, CD247, IL12RB2, **STAT4**, SCHIP1-IL12A, ATG5, **TNFAIP3**, **CSK**, **IL12RB1**
	Systemic lupus erythematosus (AHA, ATP) SC-SLE APL Monogenic SLE	AutoAb, complement AutoAb AutoAb AutoAb	DNA, Sm, ribosomes, red cells, platelets, etc. Ro/SSA, La/SSB Phospholipids, β2G Various	DRB1*1501 DRB1*0301 DRB1*1401	IRF5, **STAT4**, IFIH1, OPN, **IRF7**, **BANK1**, BLK, **TNFAIP3**, **TNIP1**, BLK, ETS1, IKZF1, **PTPN22**, ILT3 C1q, C1r/s, C2, C4A, C4B, PRKCD, DNASE1/DNASE1L3

[Only the strongest and more reproducible gene associations are shown. Gene names in bold are associated with more than one disease, and underlined when also present in autoinflammatory diseases, either the same variant (SNV) or a different variant in the same gene. For MHCII alleles, those shown with a slash mean haplotype trans-complementation, those separated by commas mean alternative associations (references in text)]

anterior uveitis. All these diseases have overlapping clinical features and often present together. Enthesitis (characteristic of AS and reactive arthritis) is often present in some forms of psoriatic arthritis and in IBD, including Crohn's disease (CD), ulcerative colitis (UC), and undifferentiated IBD. Among the vast number of gene associations to these diseases, many of them are shared (Table 23.4) and a few of them overlapping with autoimmune diseases.

AS association with the MHC class I allele HLA-B27 was the first strong HLA disease-association described (Brewerton et al. 1973) and, to date, it remains as the strongest and one of the very few associations of MHCI and disease. Nevertheless, 50 years after such finding, the role of B27 in the pathogenesis of AS and reactive arthritis remains a mystery. MHCI has essentially two functions, namely presentation of antigenic peptides to $CD8^+$ (cytotoxic) T cells and the inhibition of natural killer (NK) cell activation. None of these two functions appears to be involved in the pathogenesis of AS. Moreover, alternative hypotheses proposed to explain the apparently necessary role of B27 in AS are not easily sustainable.

23.3 The Microbiome and the Development and Tunning of the Immune System (Fig. 23.1)

Several observations indicated that environmental microorganisms are important for the development of the adaptive immune system. For instance, laboratory animals raised under sterile conditions have an increased rate of inflammatory and allergic conditions compared to animals grown in the presence of environmental bacteria. In humans, it has been shown that urban children, grown in cleaner households, are more susceptible to allergic diseases and, late in life, appear to have an increased risk of autoimmunity. This suggests that environmental microbes contribute to the build up of immune tolerance and provides the basis for the hygiene hypothesis that postulates that a normal microbiota is essential for the development of a healthy immune system (Murdaca et al. 2021). However, as we put up above, defining what is the normal microbiota is quite a challenge, as it is highly variable in different situations, in addition that a bacteria that is of benefit in some individuals may be harmful for others and this can differ depending on the presence of other associated "normal" bacteria (Rosen and Palm 2017).

Commensal bacteria interaction with the host occurs at least in four different forms: (1) Direct interaction with cells in the intestinal epithelium, such as epithelial cells (IEC), Paneth cells, absorptive epithelial cells, and goblet cells. (2) Bacterial metabolites released during their life cycle that can be absorbed and interact with many different cells and tissues. At least part of the effects of the microbiota on the immune system is mediated by bacterial metabolic products (Oh et al. 2021). (3) Interaction with cells of the immune system in the epithelial walls, either directly with non-antigen receptors or as antigens with T cells (via TCR after antigen processing) or directly by surface immunoglobulin on B cells. (4) When bacteria penetrate the epithelia, they become harmful. Because of this, these interactions are tightly restricted by an intact immune system.

Table 23.4 Features of complex autoinflammatory diseases

Group	Disease	Pathogenesis	Associated genes
Inflammatory bowel diseases	Inflammatory bowel disease	Dysbiosis of the gut microbiota, Th17-like response Type 1 interferons	CREM, CISD1, IPMK, TSPAN14, C10orf58, NKX2–3, TNNI2, LSP1, CNTF, LPXN, CD6, CCDC88B,RELA, CXCR5, MUC19, VDR, **IFNG**, GPR183, GPR18,ZFP36L1, FOS, MLH3,GPR65, GALC, SMAD3,CRTC3, **SOCS1**, LITAF,CRTC3, IL27,**IRF8**, CCL13, CCL2,ORMDL3, **STAT3**,TUBD1, RPS6KB1, SMAD7, **CD226**, **TYK2**, PHACTR2, DOK3, CCR6, RPS6KA2, ZPBP,IKZF1, SMURF1, EPO,TRIB1, JAK2,NFIL3,**TNFSF15**, CDRD9, **IL2RA**,TNFSF15, MAP3K8,CEBPG, HCK, DNMT3B, **CD40**,CEBPB, ZNF831, CTSZ, TNFRSF6B,ICOSLG, LIF, OSM, TAB1, BTBD8, SELP, SELE, SELL, MARCH7, LY75, PLA2R1, PDCD1, ATG4B, HGFAC, OSMR, FYB, LIFR, **C5orf4**, DUSP1, CNTNAP2, PTK2B, TRIM35, EPHX2, NFKB2, TRIM8, TMEM180, SH2B3, ALDH2, ATXN2, **PRDX5**, **ZMIZ1**, **YDJC**
	Crohn's disease	Dysbiosis of the gut microbiota, Th17-like response Type 1 interferons	**PTPN22**, ADAM30, **IL12B**, FASLG, **TNFSF18**, UCN, SP140, ATG16L1 IL6ST, IL31RA,**IL23R**, **REL**, **TYK2**, CPEB4, TAGAP, CREB5, JAZF1, RIPK2, LACC1,RASGRP1, SPRED1, **NOD2**,LGALS9, **NOS2**,GPX4, HMHA1, **FUT2**,**IFNGR2**, IFNAR1, USP1, PTGS2, PLA2G4A, PTPRC, PDCD1, ATG4B, IRF4, DUSP22, MAP3K7IP2, CD27, **TNFRSF1A**, **LTBR**, AKAP1, **TFSF11**, NFATC1,

(continued)

Table 23.4 (continued)

Group	Disease	Pathogenesis	Associated genes
			TST, TEF, NHP2L1, PMM1, L3MBTL2, CHADL
	Ulcerative colitis	Dysbiosis of the gut microbiota, Th17-Th1-like responses	**TNFRSF14**,RFTN2, PLCL1,**PRKCD**, ITIH4, **NFKB1**, MANBA,SLC9A3, **CARD11**, GNA12, DLD, **IRF5**,JRKL, MAML2, NXPE1, NXPE4, ITGAL, ZFP90, CALM3,ADA, HNF4A, SLC30A, EDG1, **ICOS**, **CD28**, **CTLA4**, FLJ78302, LTF, CCR1, CCR2, CCR3, CCR5, NFKBIZ, AHR
Skin/joints/ eye	Ankylosing spondylitis Reactive arthritis	Apparent dysbiosis of the gut microbiota, Th17-like response Triggered by pathogens (e.g., *Shigella flexneri*, *Campylobacter jejuni*, *Chlamydia*, etc.)	HLA-B*27:05 and HLA-B*27:02 (Caucasians), HLA-B*27:04 and HLA-B*27:07 (Asians), HLA-B*27:02 (Mediterranean populations), **PLD4**, **ERAP1**, IL1R2, ANTXR2, **IL23R**, **NOS2**, IL7R, CSF2, GPR65, **RUNX3**, ASAP2, NPM1P17, **NFKB1**, FGFR1OP, NKX2–3, **IL27**, **LTBR**, NPEPPS, ERN1, ROPN1L, SNVs*(RP11-300 J18.1, RP1-66C13.4, 16p11, 7p21, 5q33, 2q33)
	Psoriasis	Dysbiosis of the skin microbiota, Th17-like response	HLA-C*06:02, **IL12B**, **IL23R**, **TNFAIP3**,**REL**, **TYK2**, LCE3A,LCE3D, **ERAP1**, PTTG1, CSMD1, GJB2, SERPINB8, ZNF816A, CARD14,TNIP1. **JAK2**, **10q22** (**ZMIZ1**),**11q13** (**PRDX5**), 16p13 (**SOCS1**), 17q21 (**STAT3**), 19p13 (**FUT2**), and 22q11 (**YDJC**)
	Psoriatic arthritis	Dysbiosis of the skin and gut microbiotas, Th17-like response	HLA-C*06:02, HLA-B27, **IL12B**, **IL23R**, **TNFAIP3**, **REL**, **TYK2**, LCE3A, LCE3D,**ERAP1**, PTTG1, CSMD1, GJB2, SERPINB8, ZNF816A, CARD14,TNIP1 **JAK2**, **ZMIZ1**,**PRDX5**, **SOCS1**, **STAT3**, **FUT2**,

(continued)

Table 23.4 (continued)

Group	Disease	Pathogenesis	Associated genes
			YDJC, TRAF3IP2, FBXL19, **PTPN22** *TNFRSF9, LCE3A (protective associations)
	Acute (idiopathic) anterior uveitis	Apparent dysbiosis of the gut microbiota, plasmacytoid and classical dendritic cell infiltrates, Th17-like response	HLA-B27 (several others depending of the disease associated)

[Names in bold represent shared gene associations (some of them with more than one SNV in the same gene). Those underlined are also shared with autoimmune diseases. Some shared associations are in the same gene but a different SNV (references in text)]

Most of our current knowledge of microbiota deals with bacteria, but it also comprises fungus, archaea, and protozoa. Several publications have extensively reviewed the role of microbiota in the development of autoimmune diseases. Here, we focus on critical aspects of the role of commensal bacteria (symbionts) on the development and maturation of the immune system, on immune tolerance, on related changes of gene expression, and how they, under changing conditions, develop their pathogenic potential to become pathobionts (Jochum and Stecher 2020) and lead to autoimmune or autoinflammatory disease.

The first problem to deal with is to define what the normal gut microbiome is. Variables, such as geography and feeding habits have a strong influence on its composition; it is different, if you live in a rural area or in a large city. Moreover, it is not the same if you live in New York City, Paris, Mexico City, or Tokyo. This can be further complicated by the use of antibiotics that change the composition of the microbiota and lead to dysbiosis, which can be transient or long-lasting. In addition, there is a gradient in the number and genus of bacteria from the oral cavity to the rectum (de Vos et al. 2022). Bacterial number in the duodenum is much lower due to the stomach acidic environment and the duodenal presence of bile acids. After that, the number of bacteria gradually increases, as it does its composition. Hence, stool sampling must be uniform to compare one study to another. Thus, we must assume that a vast majority of the information available in human populations is somewhat speculative. Indeed, a recent study by means of hybrid, ultra-deep metagenomic sequencing (Jin et al. 2022) showed the presence of 5085 new, unclassified bacterial species in the normal human microbiome. Well controlled laboratory animals could be a means to gain insight of the role of the microbiota in the development of the adaptive immune system and possibly, to understand its relationship to human disease.

In spite all of that it is widely accepted that partly oxygen-tolerant *Firmicutes* and *Proteobacteria* are the major phyla present in the small intestine. In the colon, the number of bacteria increases exponentially and with ample predominance of anaerobic bacteria, with the Firmicutes (predominantly *Ruminococcaceae* and *Lachnospiraceae*), *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and

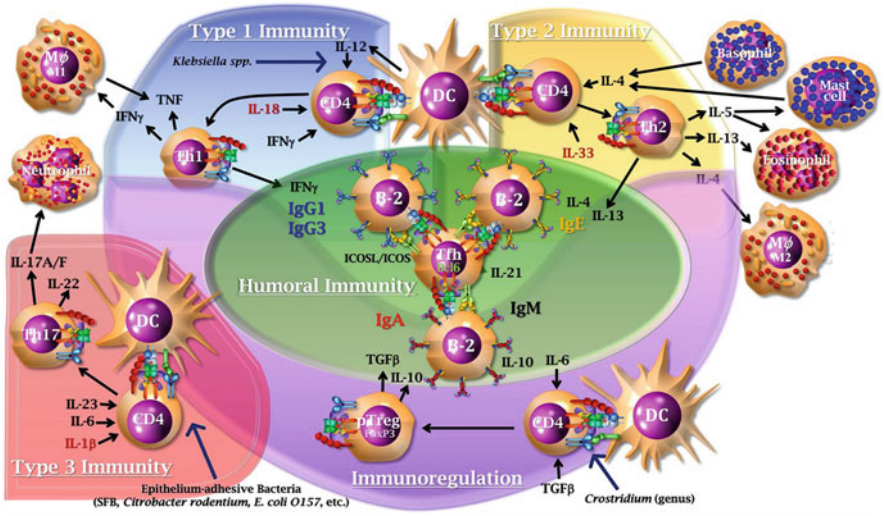

Fig. 23.1 Types of inflammation induced by differentiated T helper cells, after an initial antigenic stimulus presented by dendritic cells (DCs) in the presence of different cytokines and influence of the microbiota. For type 1 immunity (upper left, blue) Th1 cells differentiate in the presence of IFN-γ, IL-12, and IL-18 and their main cytokine is IFN-γ, which activates macrophages (Mf) to the highly inflammatory M1 subset. TNF (tumor necrosis factor) is also part of this response. Type 2 immunity (upper right, yellow) occurs in the presence of IL-4 and IL-33, and its main cytokines are IL-4, IL-5, IL-13 that together lead to differentiation and activation of mast cells, eosinophils, and the M2 subset of Mf, all of which are part of atopic responses and play an important role in tissue repair. Th17 cells differentiate in the presence of IL-6, IL-1β, and IL-23, secrete mainly IL-17 and IL-22, and coordinate type 3 immunity (lower left, red), which is highly inflammatory with neutrophils as their major effectors. Immunoregulation (bottom center, purple) is coordinated by peripheral Treg (pTreg) cells, which differentiate from other Th cells or from naïve $CD4^+$ T cells, release mainly TGF-β and IL-10 that have anti-inflammatory activity. Finally, Tfh cells coordinate humoral immunity (center, green), secrete IL-21, induce B cell differentiation, affinity maturation, and class switch recombination that depending on the cytokines released by the other Th cell subsets will be IgG1 and IgG3 (type 1 immunity), IgE (type 2 immunity), and IgA (Treg in mucoses). Type 3 immunity has no apparent role in humoral immunity. [Abbreviations: *Mϕ* macrophage, *DC* dendritic cell, *SFB* segmented filamentous bacterium]

Verrucomicrobia (*Akkermansia*) as the major phyla (Vilchez-Vargas et al. 2022). For nutrition and metabolic functions, the most important part of the gastrointestinal tract (GIT) is by far the jejunum, but for immunology, the ileum is the main organ. Therefore, the local microbiome in this area may have the biggest impact on immunity and immune-mediated diseases.

Metabolites produced by the microbiota (hundreds of them) can interact with cells of the immune system either directly or as intermediaries, through mediators released by epithelial or other cells. Of these, short-chain fatty acids (acetate, propionate, and butyrate) are of major importance. Butyrate inhibits mitogen-activated protein kinase (MAPK) pathways and nuclear factor-kappa B (NF-κB),

which modulates the release of cytokines, including IFN-γ, IL-2, IL-6, IL-8, TNF, and the action of TNF, IL-1, and IL-17 (Li et al. 2021).

Except for laboratory animals grown under specific pathogen free conditions, the immune system develops in the presence of the whole microbiota, which contains from 10^{11} to 10^{14} microbial cells, including bacteria, fungus, archaea, protozoa, and their infecting viruses. Of all the sites where bacteria interact with epithelia, the gut microbiota has a major influence on shaping the immune responses and the preferential differentiation of $CD4^+$ T cells onto functional subsets. In a series of landmark studies (Atarashi et al. 2011, 2013, 2015, 2017) it was shown that isolated gut microbiome species skew immune responses toward Th1 cells were induced by oral *Klebsiella* spp. Conversely, mono-colonization of germ-free (GF) mice or rats with *Citrobacter rodentium*, *E. coli O157,* or segmented filamentous bacteria (SFB) from mouse or rat, all of which were capable of host-specific adhesion to small intestinal epithelial cells (IEC), triggered host-specific induction of Th17 responses. Moreover, a mixture of 20 bacterial strains isolated from fecal samples of a patient with UC with EC-adhesive properties led to a robust induction of Th17 cells in the mouse colon. In the case of Treg, they are most abundant in the colonic mucosa, where spore-forming members of the microbiota, particularly the genus *Clostridium*, promoted accumulation of Treg in the mouse colon. Colonization by a defined mix of *Clostridium* strains, and even human *Clostridia*, increased levels of TGF-β and $FOXP3^+$ Treg cells' number and function in the colon. Young mice with oral inoculation of *Clostridium* were resistant to colitis. It is of importance that a great number of $CD4^+$ T cells with Treg phenotype (peripherally induced Treg or pTreg) bear bacterial-specific TCR (Li et al. 2020). Finally, broad spectrum antibiotics given early in life lead to permanent dysbiosis in the colon and affect the development of a subset of Tregs with impaired immune tolerance (Zhang et al. 2021).

Moreover, the gut microbiota shapes the immune repertoire at the B cell level, with many circulating (mainly IgG and IgA) and secreted antibodies (IgA) with specificity for bacteria of the microbiota. Thus, the bacterial composition of the microbiota can profoundly affect the course and response to the treatment of autoimmune diseases. IgA antibodies secreted in the intestinal lumen coat bacteria and limit their ability to interact with other cells and prevent their penetration into the apical membrane of epithelial cells and the invasion of host tissues (Bunker and Bendelac 2018; Huus et al. 2021; Nakajima et al. 2018; Pabst and Izcue 2022; Pabst and Slack 2020). Humans with low IgA have increased proportions of potentially inflammatory bacteria in their microbiota (Friman et al. 2002). It has been shown that IgA prevents *Bacteroides thetaiotaomicron*, a commensal bacterium, from inducing pro-inflammatory signals in the host (Peterson et al. 2007). Highly hypermutated IgA binds to and selects discrete components of the microbiota, increasing its diversity (Kawamoto et al. 2014). Moreover, local IgA antibodies specifically neutralize bacterial toxins. Thus, IgA is a regulator of the microbiome.

23.4 The Impact of the Microbiome on Autoimmune and Autoinflammatory Diseases

Through the years, several non-infectious diseases have been attributed some microbial origin. Most notable rheumatic fever has been known for many decades to develop after a *Streptococcal* infection and considered to be autoimmune. To date, there are many hypotheses but yet there is not a defined mechanism whereby β-hemolytic *Streptococcus* leads to rheumatic fever. In the early twentieth century, at least in France, RA was considered as a form of tuberculosis. Some others proposed later that *Mycoplasma fermentans* could be the etiologic agent of RA, and latter it was attributed to some viruses, until the hypothesis of a single infectious agent in the etiology of RA was abandoned in the 1980s [Reviewed by (Moreno 2015)]. Among the main mechanisms invoked for the role of infectious agents on autoimmunity was molecular mimicry (Oldstone 1987; Qiu et al. 2019), which to date still suffers of lack of evidence for most diseases, apparently except for multiple sclerosis (MS) patients, many of which have a history of infectious mononucleosis. Antibodies directed at Epstein Barr virus nuclear antigen 1 (EBNA1) in these patients are cross-reactive with the glial adhesion protein Glial CAM (Lanz et al. 2022), which constitute the most striking example of molecular mimicry in autoimmunity to date.

Nevertheless, the increased rate of certain clinical infections in patients with early but not with established RA was noted since 1924 (Billington and Crabbe 1924). Additional indirect evidence is the improvement of RA in response to antibiotics, particularly in patients with early disease (Stone et al. 2003). The modern view of the effects of microorganisms in the development of autoimmune disease is the microbiota. Unfortunately, the many contradictions in the corresponding literature do not allow to safely arrive at a sustainable hypothesis. What we refer here in that regard must be considered mostly anecdotal, but it should provide sufficient basis to support further studies.

Early excess of proteobacteria, loss of *Bifidobacterium* and dysbiosis of the gut microbiome (Duar et al. 2020; Shin et al. 2015), leads to chronic immune dysregulation and to atopic conditions (Arrieta and Finlay 2014; Laforest-Lapointe and Arrieta 2017), as well as autoimmune or autoinflammatory conditions (Hviid et al. 2011; Vatanen et al. 2016). Analysis by means of 16S rRNA sequencing of the colon microbiome of patients with autoimmune diseases, including celiac disease (CeD), RA, multiple sclerosis (MS), Sjögren's syndrome (SS), and T1D, showed dysbiosis in all with a uniform decrease in *Prevotella* genus in MS patients (Marietta et al. 2020).

The mucosal barrier is also important to keep the microbiota, including commensals, at bay. In addition to the epithelium itself, the composition of mucus has been shown to prevent bacterial colonization and IBD. This includes mucus sialylation, protein glycosylation, and other post-translational modifications (Irons et al. 2022). Unfortunately, there is not a consistent manner to correlate human genetic variations with specific compositions of the microbiome (either 16S rRNA or metagenomic sequencing) yet. Although a few studies have claimed some

associations, these have not been widely reproducible, except for two loci: LCT (encoding the enzyme lactase) and *Bifidobacterium* and two independent SNVs in the ABO locus (which determines the blood groups) that are associated with the abundance of *Faecalibacterium* and *Bacteroides* in Germans, Finnish, and Dutch people (Sanna et al. 2022). Moreover, only one of the genes proposed to have some influence on the microbiome (CD5) is of immunological relevance but it is not known to have variants in association with autoimmune diseases. Additional reported associations of gut microbiome dysbiosis with autoimmune diseases are RA with *Prevotella copri*, T1D and CeD with *Bifidobacterium genus* (Xu et al. 2021).

It is known that IL-10 signaling is highly relevant for some patients with IBD, and loss-of-function mutations in the IL-10 pathway can cause IBD in children under 6 years old. Other IL-10, IL-10RA, and IL-10RB variants are also associated with adult onset IBD. As mentioned above, the microbiota strongly influences Treg development and compartmentalization, which affects local IL-10 production and susceptibility to IBD and, possibly, other autoinflammatory diseases [reviewed in (Jacobse et al. 2021)]. However, we must keep in mind that the many contradictory results in the literature complicate the task of defining disease associations with microbiota, at least for the present time. Table 23.5 contains some examples of selected studies of the microbiome in human autoimmune and inflammatory diseases.

Studies in a mouse model of RA showed the transmission of an inflammatory phenotype to GF mice transplanted with fecal matter from murine donors with experimental RA and IBD. The dysbiosis of murine donors with inflammation was transmitted to GF mice, but not to mice with a healthy microbiome regardless of their genetic background, indicating that a healthy microbiome can resist colonization by a dysbiotic microbiome of *Lactobacillus*, *Escherichia*, *Bacteroides*, *Parabacteroides*, *Helicobacter*, *Clostridium*, *Eubacterium*, *Actetanaerobacterium*, *Lachnoclostridium*, *Roseburia*, *Prevotella,* and *Oscillospir* (Edwards et al. 2021).

23.5 Conclusions

Most autoimmune and autoinflammatory diseases are complex conditions where genetic and environmental factors contribute to trigger an enhanced and uncontrolled inflammatory response.

During the last few years, mainly based on systems biology studies have allowed a much better understanding of the nature of autoimmune and autoinflammatory diseases. This has opened the gates for new therapeutic approaches, such as the kinase inhibitors to treat autoimmunity. Although there is still a long road to go, we are beginning to get some insight into the role of the microbiome on the development and maturation of the immune system and the shaping of the T and B cell repertoires. In a near future, the use of probiotics, microbe transplants, as well as special diets and a rational use of antibiotics, will provide a new therapeutic arsenal that added to

Table 23.5 Gut microbiome studies in selected autoimmune and autoinflammatory diseases

Disease		Gut microbiome			
		Increased	Decreased	Consequences	References
RA		*Prevotella copri* (species)		Early onset RA	Scher et al. (2013)
		Megamonas, *Monoglobus*, *Prevotella Verrucomicrobiota Firmicutes*	*Bacteroidota*	↑CD4+ Th1, Th2 cytokines ↓Treg ↑activity ↑Treg ↓Th17	Wang et al. (2022).
		Porphyromonas gingivalis (mouth)	*Bacteroides*, *Faecalibacterium*, *Hemophilus*	Triggers autoimmunity? ↑disease activity	Kharlamova et al. (2016)
SLE		*Bifidobacterium*, *Ruminococcus*		↓ Disease risk	Xu et al. (2021)
T1D		*Bifidobacterium*		↑ Disease risk	Xu et al. (2021)
CeD		*Bifidobacterium*		↑ Disease risk	Xu et al. (2021)
IBD	IBD	*Ruminococcus gnavus* Short-chain fatty acid-producing anaerobes (*Bifidobacterium*, *Roseburia*, *Clostridium, Lachnospiraceae*, *Prevotella*, *Ruminococcus*)		↑ Disease risk Improvement after fecal transplantation	Hall et al. (2017) Mocanu et al. (2021)
	CrD	*Proteobacteria* (*Escherichia, Ruminococcus gnavus, Cetobacterium, Actinobacillus, Enterococcus), Faecalibacterium, Coprococcus, Prevotella and Roseburia*	*Firmicutes*, *Bacteroidetes*, *Faecalibacterium*, *Coprococcus*, *Prevotella*, *Roseburia*		Nishino et al. (2018)
	UC	*Bacteroides vulgatus* proteases		Disease severity	Mills et al. (2022)
AS		*Clostridia* (*Veillonellaceae*) *Proteobacteria* (*Brucella* spp. *Campylobacter concisus*). (Saliva)	*Streptococcus*	↑ sIL-6Rα, IL-2, IL-10, IL-11, IL-12p40, IL-12p70, IL-20, IL-26, IL-27, IL-28A, IL-29 (IFNα, IFNβ, and MMP-3 (matrix metalloproteinase 3)	Lv et al. (2021)

conventional treatments will allow better outcomes for patients with autoimmune diseases.

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Current Challenges in Research with Exploring the Microbial Pathomechanisms of Autoimmune Diseases

24

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Abstract

Understanding the mechanisms responsible for the induction of autoimmune diseases is not an easy task given that the close interplay between environmental factors, mainly pathogens, and the immune system is difficult to explore at the preclinical setting. Most studies investigating the role of infectious triggers are largely limited at the level of experimental animal models. Investigations of the microbiome in clinical samples from patients suffering from autoimmune diseases are emerging, providing a plethora of informative data, but most of them have been acquired long after the disease onset and are unable to provide useful hints regarding early or very early immunopathophysiological changes. Moreover, inconsistent results obtained among studies, largely attributed to the lack of standardized techniques and biased sampling, have made interpretation of the obtained data less proper. Nevertheless, advances in technology and experimental methods have led to the appreciation that the -omics era will provide the exponential growth of big data needed to uncover the hidden mechanism responsible for the likely involvement of infectious triggers and the close interplay between the microbiome and immune system, which is responsible for the loss of

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immunological breakdown and the development of autoimmune diseases. This chapter discusses the challenges the scientific community must face, so that future endeavors may eventually overcome them, including the need for well-designed, large, longitudinal studies.

Keywords

Autoantibody · Autoimmunity · Autoimmune disease · Immune cells · Infection · Infectome · Immunity · Lymphocytes · Microbiome · Microbiota

24.1 Introduction

The symbiosis of humans and microbes has been known for hundreds of years, though the importance of their co-existence has only recently begun to be understood. In humans, microbes develop in several systems, such as the skin, the respiratory tract, and particularly the intestinal tract. Different microbial strands and species develop in the various sites, all accommodating the potential of interacting with the host organism and influencing many physiological processes, especially regarding the immune system. As we have analyzed in the present book, their implication in pathophysiological processes and even autoimmune diseases has been highlighted by several studies in the last years. Additionally, these microorganisms interact with each other as well, either competitively or synergistically, and as such, the human microbiome is characterized by its tremendous complexity (Foster et al. 2017).

Advances in technology and experimental methods have significantly aided in promoting microbiome-related research. For example, new high-throughput sequencing techniques such as the analysis of 16S ribosomal RNA (rRNA) paved the way for the field of genomic and metagenomic sequencing analyses, which helped research move past bacterial culture, allowing scientists to identify the microorganisms and their respective functions with greater ease. The term human metagenome now refers to the sum of *Homo sapiens* genes, and the genes of all the microbes that have colonized the human organism, which are thought to encode at least 100 times more unique genes than just the human (Ley et al. 2006). From there, other "meta-" branches have sprung, going downstream from the genetic components, to the end products, as we shall analyze below.

These advances have led to the exponential growth of research in the field, as there is an obvious increasing trend of publications on the matter during the last 20 years, and of good quality, with a particular focus on intestinal diseases and obesity (Huang et al. 2019). In fact, human microbiome research is now receiving important funding, which only highlights the growing interest towards this field (Team NIHHMPA 2019). However, in order for future research endeavors to be more fruitful and their results regarding human diseases more accurate, several issues and pitfalls that have surfaced need to be addressed. Matters such as the need of multidisciplinary teams, identifying the true function of the microbiome, and

the interactions between microbiota and drugs, diet, and other external or internal factors, are all challenges that research currently faces. In this chapter, we present and discuss these challenges, so that future endeavors may eventually overcome them.

24.2 Unanswered Questions Regarding Symbiosis

Scientists have delved deep into how disturbances in gut microbiota may lead to autoimmune disorders, or vice versa, even though basic questions regarding the symbiosis between humans and microbes remain unanswered, and as such, many of the hypotheses that are made and tested in research may be expressed under conditions that are mistakenly accepted as true and thus be somewhat misguided.

The emergence of symbiosis dates back to several millennia ago, when organisms evolved together, by providing mutual benefits. However, numerous questions arise when one considers the complexity of these interactions, which cannot solely be understood under the concept of benefits. As such, host-to-microbe, microbe-to-host, and microbe-to-microbe interplays need to be more closely examined (Foster et al. 2017).

For humans and mammals, microbiota offer myriads of benefits, from providing essential nutrients and vitamins, to defending against pathogens. They are even known to promote immune system development and maturation (Mazmanian et al. 2005); in fact, some recently described lymphoid cells even require the microbiota in order to gain their tissue-specific function (Thaiss et al. 2016). Nevertheless, the concept of benefits for the host is not that simple, since a benefit for the host could mean cost for the microorganism and not benefit its own survival in the long run, especially considering how millions of microbial species compete inside the host's microenvironment. As such, based on the principle of natural selection, a benefit for the host in this sense would not be preferred, as the microbial strain would soon perish. It is therefore more likely that host and microbiota follow different selection procedures and do not necessarily consist one evolutionary unit (Foster et al. 2017). The benefit concept is further challenged by the existence of known pathogens within the beneficial flora (Buffie et al. 2015), although these consist the exception, since most of the encountered species are non-pathogenic and exert some sort of direct or indirect benefit.

Conversely, hosts need to tightly regulate their microbiota (Schluter and Foster 2012) and possess several ways, and reasons, of doing so. Firstly, the host can control which microbial species and strains are allowed in each epithelial site, via innate and acquired mechanisms, such as stomach acidity and avoidance of rotten alimentation (Foster et al. 2017). The epithelium, the mucus, and numerous antimicrobial factors aid in keeping certain organs and sites sterile (Hooper et al. 2012), and the host organism can monitor its microbial population, promoting their survival or their extermination. Pattern-recognition receptors of the host respond to structures preserved on pathogens and microbes, and the host can modulate its reaction against them; for instance, in cases of intestinal epithelium rupture or cell damage, this

reaction is markedly increased (Vaishnava et al. 2011). Moving on, the host can further monitor the "benefits" it receives, such as anti-inflammatory substances, in order to promote the proliferation of bacteria that produce it in case it finds them reduced (Arpaia and Rudensky 2014). Besides beneficial substances, the host may also recognize antimicrobial peptides, performing the so-called genotype-based discrimination, in order to track which strains proliferate in a given instance. This lacks the ability of pinpointing when an otherwise beneficial bacterium develops a malicious phenotype (or the other way around), but adaptive immunity, accumulating information after infections, can cover that gap and influence microbiota (Kato et al. 2014; Foster et al. 2017).

Of course, the study of the immune system has mostly focused on the "negative" reactions against pathogens, so research on the "positive" ones has been largely sidetracked, even though they may hold great significance for symbiosis (Schluter and Foster 2012). It is possible that several links to autoimmunity may be hidden behind these "positive" reactions, as to why some bacteria tied to such diseases are left or even encouraged to proliferate. Additionally, research on the effects of the microbiome on the innate immune system has been relatively sidetracked, and many more bacterial species than once perceived are thought to play a part that still remains undiscovered. Because the innate immune system does not act in an antigen-specific manner, it is likely that it assesses microbial activity in a more generic way, as a whole (Thaiss et al. 2016). The mechanisms behind this, i.e. which microbial traits or products signal the innate immune system, remain elusive, despite potentially holding key answers to microbe-induced diseases, also possibly autoimmune ones.

Finally, the microbe-to-microbe interactions are extremely versatile and complicated. From their own nature, bacteria compete against each other for survival via various mechanisms, though when forced to coexist within another host, their interplay becomes much more intricate, especially when under the strict regulation of the host.

As such, in order to understand the proper function of the microbiome, research should not focus solely on the potential benefits that microbes offer to host, but rather apply a holistic approach, taking into account all the challenges that microbiota face, both from other microbiota and the host itself (Foster et al. 2017). Defining what consists a "healthy" microbiome, and why the immune system works to preserve or tolerate it, is still a feat largely unaccomplished (Thaiss et al. 2016). In this regard, the development of standards in microbiome research is of paramount importance: analytical standards for the quality of the readouts, technical procedure standards for sample processing, and annotation standards for integrating the results of different research groups and studies (Tripathi et al. 2018). These standards are greatly lacking in this research field and are urgently needed, since gaining a deeper understanding of the "healthy" microbiome's function and coping mechanisms will also provide insight into its disturbances, and their possible sequelae, such as autoimmune diseases, and may even give rise to ideas regarding prevention or treatment of such disorders.

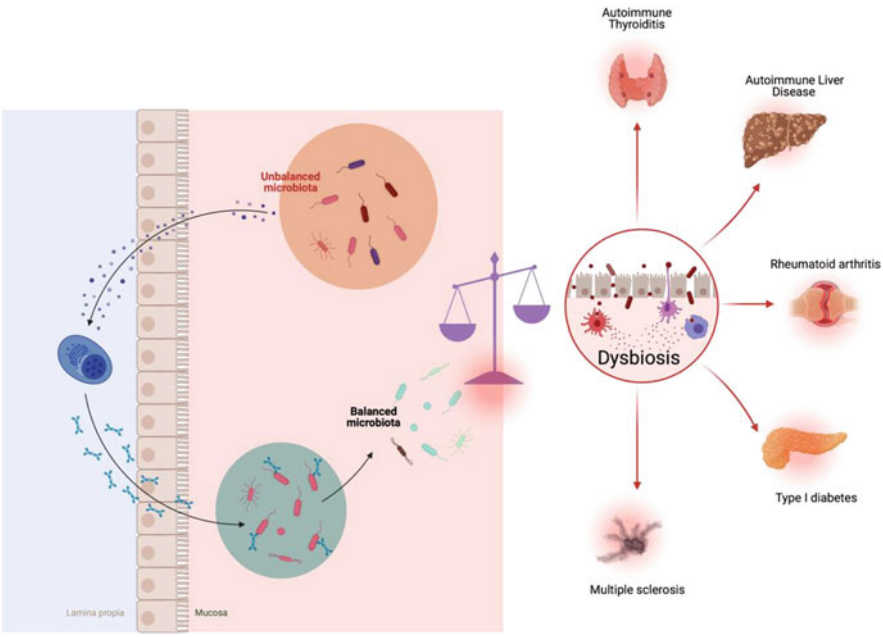

Fig. 24.1 Dysbiosis: a state of unbalanced microbiota status. Dysbiosis has been considered instrumental for the induction of autoimmunity and autoimmune diseases (*prepared using BioRender under license to DPB*)

In this train of thought, "dysbiosis," the term used to describe alterations in the gut flora in the context of a disease or other exposure is also at times poorly defined in studies. It could refer to differences in the biological variety within a sample, differences in microbiome composition within samples, in the relative abundancies of species/taxa, or any combination of these (Debelius et al. 2016). Any of these may truly reflect important changes, but comparing studies with different senses of dysbiosis becomes particularly tricky.

Moving on, another question arises when one fathoms the interplay between medications and the microbiome, which shall be analyzed in more depth later. It is known that reciprocal relations exist between drugs and microbiota; drugs affect microbiota populations and functions, while the microbiome influences the action and bioavailability of numerous therapeutical agents. Elements of dysbiosis, described in several autoimmune disorders, have been shown to subside upon effective treatment (Yamamoto and Jorgensen 2019b), though whether this is a direct result of the medication, or the consequence of reduced inflammation, still remains unclear. This represents another "the chicken of the egg" question; is dysbiosis the trigger of inflammatory procedures and autoimmunity, or is it rather a result of these processes? (Fig. 24.1). The complexity of autoimmune diseases also disallows a safe answer to this dilemma, which could hold vast significance in understanding and potentially curing them.

24.3 Confounding Factors

The microbiome is a dynamic system, which presents alterations as a response to several stimuli, both internal and external, and even shows circadian rhythm fluctuations (Thaiss et al. 2014) and changes within different periods of a year, in the same individual (Tripathi et al. 2018). The various factors that influence the microbiome may be also implicated in autoimmunity, though the mechanisms of this interaction are far from elucidated.

Starting from the building blocks of the host organism, gut microbiota composition seems to be affected to a considerable degree by the genetic background of an individual. Several microbial taxa linked to various disorders can be heritable, and their relative abundance is dictated by specific genetic polymorphisms (Lim et al. 2017; Goodrich et al. 2014b). Autoimmune diseases also present strong ties to particular polymorphisms and especially to class II human leukocyte antigen (HLA) alleles. It has been shown that HLA risk or protective loci are associated with alterations in gut flora, by influencing the populations of protective or pathogenic/autoimmune-triggering species (Russell et al. 2019). However, very few human studies exploring the relationship between genetic polymorphisms, microbiota, and autoimmunity exist in humans. Besides this paucity, explaining how genetic polymorphisms affect the microbial populations is also challenging, and mostly speculations have been expressed so far. On the other side, animal studies have even shown that particular species affect the expression of genes involved in multitude of intestinal functions (Thaiss et al. 2016), further perplexing the gene-microbiome matter.

A step further than genetics, microbiota seem to influence epigenetic modifications as well. For example, it is postulated that microbial metabolites affect histone modifications, with some of the affected pathways belonging to immune processes (Thaiss et al. 2016). This implication in epigenetic modulations could hold the key to identifying the mechanisms behind microbial influences on the host organism, though much more research is required in this direction.

Diet seems to be a major player in microbiota and autoimmunity processes (Vieira et al. 2014), given how the immune system is vastly dependent on the nutrition status and the metabolism of an individual (MacIver et al. 2013). Dietary restriction is considered to have anti-inflammatory effects and to aid in preventing or delaying the processes of several autoimmune diseases (Choi et al. 2017). However, the effects of caloric restriction on gut microbiota have not been as studied, and as such, science cannot prove or deny that this positive effect of diet on autoimmunity stems from a direct effect of the diet on the immune system or via alterations in gut microbiota, which in turn regulate immune processes (Vieira et al. 2014). Additionally, differences in microbiota composition between obese and lean subjects do exist, such as in the abundance of specific species (Lim et al. 2017), and the "obese" microbiome has a tendency to increase caloric intake from the diet (Turnbaugh et al. 2006); as such, it is possible that a certain microbiome phenotype, e.g. that in obese subjects, may drive autoimmune processes. Again, though, the mechanisms behind this interplay remain poorly understood, especially regarding autoimmune diseases

unrelated to the intestinal system. Furthermore, it is known that long-term diet has a greater effect on the microbiome, between different populations and individuals than short-term alimentary habits, but many studies concentrate on these short-term changes and may ultimately "miss" the greater picture (Tripathi et al. 2018).

A specific mention should be made to vitamin D. Besides its well-known function in calcium and bone metabolism, it is also crucially involved in immune processes, seems to possess anti-inflammatory properties, and the vitamin D status of an individual has been tied to autoimmune disorders (Yamamoto and Jorgensen 2019a). Recently, this vitamin D status was also linked to gut flora composition, with low vitamin D activity denoting higher gut barrier permeability and thus higher rates of immune system interaction with microbiota (Yamamoto and Jorgensen 2019b). Given the fluctuations that vitamin D levels may have during the course of life of a person, for example, due to alimentary habits or sun exposure, it is important that this factor also be accounted for when assessing the microbiome and autoimmunity.

Moving on, microbiota interact not only with the host, but with other environmental factors as well, microorganisms included. The discussion has recently turned towards viral infections, which have long been tied to autoimmunity, or even the symbiosis of humans with viruses, and the term "virome" has been introduced. It has further been shown that the virome varies heavily between individuals, regardless of genetic similarities, but remains remarkably stable within the individual itself (Reyes et al. 2010). Defining the intestinal virome has been made possible via technological advancements in the last years, though many challenges and methodological limitations still exist, such as identifying viruses via genome, based on sequence similarity with sequences from other databases. This means that a large percentage of the virome cannot be identified (Moon and Stappenbeck 2012). Additionally, intestinal bacteria are known to regulate the host–virus interaction; they can inhibit viral infections (Varyukhina et al. 2012), promote and sustain viral proliferation (Kuss et al. 2011), or even induce a bacterial infection, following the viral one. However, these mechanisms also remain largely elusive. Given the importance of infections as possible triggers in autoimmune diseases (Bogdanos and Sakkas 2017), the interplay of the gut microbiome and viral infections needs to be further addressed, since promoting bacteria that hinder the growth of known viral instigators could eventually prevent certain autoimmune disorders, such as rheumatoid arthritis (Fig. 24.2). Ourselves suggested that the appreciation of the complex sequel of events, what we defined as "infectome" and "autoinfectome," which implicates the microbiome-dependent infectious triggers causing autoimmunity, will be difficult to define and explore at the preclinical setting (Bogdanos et al. 2013a, b).

24.4 Technical Difficulties

Not all bacteria are as easy to cultivate in a laboratory, and several species that inhabit the human body and the intestinal tract in particular are especially challenging in this regard, with some only recently having finally been cultured (Lagier et al.

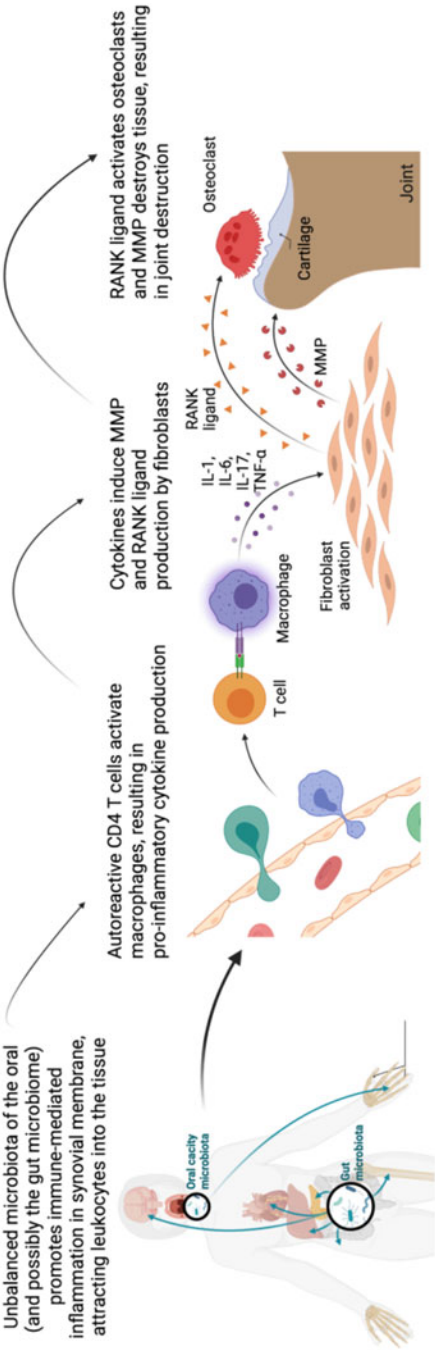

Fig. 24.2 Role of oral and gut dysbiosis in the development of rheumatoid arthritis (*prepared using BioRender under license to DPB*)

2016). Additionally, stool samples, used in a plethora of studies, do not accurately reflect what is happening within the host organism and at the truly important host–microbe interface; intestinal mucus sample is better in this regard, but comes with all the challenges of acquiring such samples (Garber 2015; Yamamoto and Jorgensen 2019b). New cultivation models are being introduced, attempting to combine the culture of human and microbial cells together in order to more accurately replicate the in vivo conditions (Shah et al. 2016).

It was with the development of the "-omics" approaches, such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics, that the field of microbiome research has blossomed. These, besides identifying species and strains, also identify metabolites and metabolic pathways possibly implicated in autoimmune processes and thus provide ideas for microbe-targeted pharmaceutical interventions (Zhang et al. 2019). However, these approaches have their own issues that need to be overcome.

Metagenomics, sequencing the entirety of the genetic code of host and microbial cells, now employ next-generation sequencing techniques, such as 16S RNA gene analysis and shotgun metagenomics. Of note, 16S RNA analysis does not target the entirety of the genome and is thus considered not to entirely belong to the "metagenomics" branch by some (Quince et al. 2017). Shotgun metagenomics can provide whole genome sequences, taxonomic classification, and functional information of the various microbes. Nevertheless, despite its relatively simple design, it can be riddled with several issues. Besides being expensive and requiring access to advanced facilities, due to numerous experimental steps and available methods, it is subject to various biases, and these methods, alongside the sequencing and library development platforms, carry their own inherent limitations (Quince et al. 2017; Nelson et al. 2014).The depletion of host genetic material is also often required because it can dominate the samples (Tripathi et al. 2018). Furthermore, functional profiling is hindered by intrinsic microbial factors that influence quantitative assessment (Beszteri et al. 2010) and by the lack of accurate annotations of a plethora of genes. This extends to the issue of the "microbial dark matter," where several microbiota remain unidentified. Metagenomic methods help in identifying them, but basic questions about the nature of the discovered species, such as their metabolic needs and survival conditions, cannot be answered through them (Dance 2020). Additionally, the identification of pathogenic species that are not part of the gut flora, or the identification of free nucleic acid that persists even when the cell it came from has died, lowers the accuracy of metagenomic approaches (Quince et al. 2017). Finally, in all these types of studies, acquiring proper control samples represents a major challenge, due to existence of numerous influencing factors, as we mentioned above. To address this, longitudinal studies assessing samples from the same habitat over various time points are recommended over simple cross-sectional studies (Knight et al. 2012).

Given that not all genes of any given organism are transcribed and are thus functionally relevant, metatranscriptomics goes one-step further than metagenomics, applying similar analytic techniques and adapting the respective metagenomic software. Metatranscriptomics can be combined with metagenomics, providing

several benefits, such as discriminating dead or inert microbiota from active ones, based on their transcriptional activity. Assessing this activity can also denote whether the function of specific species is being induced or repressed under certain circumstances. However, these analyses are dependent on the acquisition of adequate high-quality RNA samples, a feat rendered challenging by the high activity of RNases in host tissues. In addition, the abundance of other transcripts, such as ribosomal proteins, non-coding RNA, and translation factors, or transcripts of more abundant species could obstruct the detection of important but expressed to a smaller degree transcripts (Zhang et al. 2019).

Metaproteomic studies focus on the produced proteins, mostly via means of mass spectrometry. In theory, this approach provides higher quality insight on the function of gut microbiota, since it overcomes the issue that metatranscriptomics face that not all transcripts are ultimately translated into proteins. Practically though, it faces several issues. Firstly, the high degree of complexity of proteomic analysis requires computational systems with very big drives and memory capacity and complicated algorithms; as such, various software and hardware issues may arise (Heyer et al. 2017). Furthermore, homologous proteins, carrying the same amino acid sequences but different stereotactic structure and function, cannot be differentiated, and therefore an important piece of information is lost (Herbst et al. 2016). Metaproteomics also make use of existent protein databases; this means that detecting previously unidentified proteins, or proteins not included in a given dataset, is difficult. Since small differences in genotypes can lead to important differences in a protein structure and therefore its identification, even within similar microorganisms, the combination of metagenomics with metaproteomics has started to gain more ground. New metaproteomic workflows, software, and libraries are being developed (Heyer et al. 2017), and since it is still a relatively new field, proper guidelines and recommendations have only recently started to appear, on the hopes of improving the quality and accuracy of the results of this promising method (Zhang and Figeys 2019). Finally, metaproteomics present smaller measurement rates than other -omics approaches, reaching up to 20% of the proteins present in human gut microbiota and losing several of those expressed in a relatively low abundancy due to spectrometry saturation from proteins expressed in high quantities from more dominant species (Zhang et al. 2016); steps towards developing methods to overcome this are being taken (Mayers et al. 2017).

As previously mentioned, the microbiome plays a crucial role in host metabolism, and so the metabolomics were introduced. The metabolome, i.e. the entirety of chemical entities implicated in the metabolism, was firstly studied on the hopes of identifying disease biomarkers, but has steadily gained more interest, since it can be used to reveal important biological processes in health and disease. Additionally, the metabolome is known to influence the rest of the "-omics" (Rinschen et al. 2019), and metabolites can actively alter cellular physiology and impact immunity (Liu et al. 2017), thus also possibly pertaining to autoimmunity. The metabolomics approach makes use of techniques such as mass spectrometry and nuclear magnetic resonance spectroscopy to identify metabolites in the gut flora. Much like other "-omics," metabolomics require access to expensive and specialized laboratory

equipment and bioinformatic tools (Rinschen et al. 2019) that are not readily available, while there is a general lack of related data libraries and sharing methods, which has only recently started to be addressed (Sud et al. 2016). The chemical diversity of the studied molecules also adds to the difficulty, due to the need for the proper selection of solvents, machinery, and data analysis processes (Tripathi et al. 2018). Moving on, identifying the most important metabolites for a given context, and their biochemical functions, remains challenging, while further pinpointing the origins of a given metabolite, i.e. whether host or microbe, and attributing to specific species or taxa constitute major issues of metabolomics as well (Zhang et al. 2019; Rinschen et al. 2019).

The aforementioned issue of the databases is present in all the "-omics" approaches, such as in the case of the microbial "dark matter." Species or molecules that have come up in studies but cannot be matched to an existent database are often disregarded, and so potentially crucial pieces of information are lost. These databases often contain items from biased sources, such as species from studies on pathogenic species or molecules from commercially available products, and consequently, a limited portion of a given study's results may be interpreted and used (Tripathi et al. 2018; da Silva et al. 2015).

All in all, the "-omics" have plenty to offer for the field of microbiome research, and especially in tying microbiota to autoimmune diseases. However, there are numerous technical difficulties and a difficulty in interpreting the yielded results, or understanding whether they hold some significance or not. It is encouraging to notice that there are several initiatives being launched, to facilitate research in this direction and tackle the aforementioned issues.

Finally, the discrepancies between studies also need to be addressed, since technical factors of variation can influence the yielded results to an extent that mimics that of biological ones (Debelius et al. 2016). From sample type and collection, to primer use, to the analytical and statistical methods applied, there is great heterogeneity in the available literature, and not all methods of choice are the gold standard. For instance, in fecal samples, ideal storage should be kept at a −80 °C temperature. Other preservation methods exist, some better than others, but it is known that preservation exerts a significant effect on microbial communities and should not be taken lightly (Sinha et al. 2016; Debelius et al. 2016). Similarly, DNA extraction methods can also alter the results (Wesolowska-Andersen et al. 2014), with the use of primers and fragments creating different biases in each case (Debelius et al. 2016).

24.5 The Multiomics Approach

As an attempt to cover the understanding gaps stemming from the results of each separate "-omic" method, the multiomics approach was proposed; integrating and correlating data from a multitude of these methods is postulated to provide important additional information. A combination of transcriptomic, proteomic, and metabolomic data sets has already been introduced in various research fields,

autoimmune diseases included (Lorenzon et al. 2018), as a way to identify overlaps between metabolites and transcripts/proteins, better describe functions and dynamic alterations in these systems, and serve as an add-on to pathway analysis (Rinschen et al. 2019; Zhang et al. 2019).

However, this integration is not an easy feat. First of all, acquiring the desired datasets from each approach is challenging on its own, and their integration is usually performed without a predefined strategy. This is further hindered by inherent biases stemming from the individual "-omic" datasets and especially the fact that they are usually products of different laboratories, so there could be a significant element of technical heterogeneity, besides the other biological, chemical, physical, and other inherent factors that add to this heterogeneity (Haas et al. 2017). In addition, other technical issues, such as noise removal, artifacts, identifier matching, model validation, and finding the appropriate computational and mathematical methods further add to the challenge (Rinschen et al. 2019); multiomics are vastly dependent on advanced bioinformatic and statistical tools, such as machine learning (Zhang et al. 2019). Lastly, not every piece of available "-omics" data is always used properly in order for accurate results to be drawn. As such, deriving to a functional conclusion from descriptive data still represents the major challenge in multiomics (Haas et al. 2017), despite it being a very promising research field that will possibly answer several questions that have risen through the research on microbe and autoimmune and other disorders.

24.6 Drug–Microbiome Interactions and Translatability

It has been shown that non-antibiotic pharmaceutical agents can have a considerable effect on the gut microbiome and its composition (Maier et al. 2018), and correspondingly, the host microbiome seems to also affect the metabolism of drugs—for instance, by degrading it or by regulating the enzymes that metabolize a drug (Guthrie and Kelly 2019)—and how the organism responds to treatment overall (Zhang et al. 2019). For instance, it has been reported that metformin, a commonly prescribed medication against diabetes mellitus, provides its therapeutic effects possibly also due to the induced alterations of the gut flora (Wu et al. 2017). Additionally, several regimes depend on the bacteria metabolizing a pro-drug, and turning it into the active compound (Kuntz and Gilbert 2017). Consequently, the microbiome interacts heavily with medication and may eventually be the target of interventions, though the understanding of drug–microbiome interactions remains incomplete, and thus exploring this option requires much more research. In fact, very few drugs have been included in datasets recording these interactions (Saad et al. 2012), and the insight provided does not always denote whether the interaction is of clinical importance or miniscule and either positive or negative (Zhang et al. 2019). As such, platforms to properly assess their interplay are still lacking and needed.

The ultimate goal of any research endeavor is to eventually help in treating or preventing disease, by understanding both the physiological and pathophysiological processes. The translatability regarding microbiome research is another issue that

further needs to be addressed. It is understandable by now that the microbiome plays a crucial role in several key pathways of an organism, is involved in numerous disorders, and further affects drug metabolism and response to treatment. It is now even considered a possible target for interventions. However, the way until precision medicine involving the microbial composition of each patient is far from paved.

Firstly, the traditional laboratory culture methods have not been very effective in this burgeoning research field. Enteroids and organoids consist an alternative, but may require a significant amount of time to stabilize and are not ideal for the cultivation of anaerobes (Guthrie and Kelly 2019). Besides in vitro methods, animal models, alongside being expensive, ethically ambiguous, and time-consuming, do not always accurately predict what eventually happens in humans (Zhang et al. 2019). Mouse models are the ones most commonly applied, due to several similarities with humans, but carrying important differences as well, in both anatomy and physiology (Guthrie and Kelly 2019). Additionally, they carry their own confounding factors, such as the so-called maternal effect, where inoculation time in infantile mice affects their microbiome in a way that can span generations, the existence of coprophagy in rodents that share the same cage, and various environmental conditions that differ between keeping facilities and are known to affect bacterial composition (Goodrich et al. 2014a). However, new techniques, as previously mentioned, are trying to emulate real-life conditions, with some paying particular attention to drug–microbiome interactions, by integrating -omics approaches into bacterial culture (Li et al. 2020). A comparison of in vitro findings with those from in vivo studies can also be attempted (Maier et al. 2018), but this method mostly serves as a confirmation of the in vitro results, which are often poorly representative of real-life conditions.

Moving on, regarding drug metabolism from bacteria and how they respond upon exposure to numerous regimes, there is significant variation between individuals. In the case of medications requiring activation via bacterial metabolism, the bioavailability of the drug is dictated by the microbiome composition of an individual. As such, the dosage of drugs with very specific therapeutic windows needs to be tailored to an individual's intestinal microbiome composition; precision medicine, as it is called, seems to be the future of microbiome research, in applying the knowledge acquired to properly administering treatment. Furthermore, potential side-effects are also linked to the gut flora and its specific strains, while harmful compounds can be released when some bacteria are exposed to particular substances (Kuntz and Gilbert 2017). However, there is a general paucity of studies assessing these effects, and, as previously mentioned, in vitro findings may not always accurately recreate the in vivo conditions, where a plethora of confounding factors are at play. Additionally, the existence of reciprocal associations between drugs and microbiota, i.e. the change of gut flora composition due to pharmaceutical substances, and the indirect interaction of medication and bacteria, for instance, due to their effects on the immune and the endocrine systems, further hinder the proper definition of drug–microbiome interactions and their consequent application in treatment algorithms. Finally, another obstacle is met in pinpointing which microbiome traits that have come up in preclinical trials may serve as useful endpoints in a clinical setting; the

presence and levels of a certain species or enzyme in the studied samples may not accurately reflect the metabolism of a compound. As such, machine learning approaches, encompassing and combining a multitude of high-potential traits, clinical and laboratory, will need to be applied (Guthrie and Kelly 2019), with all their inherent challenges.

Given the burden that autoimmune diseases confer to patients and society as a whole, a substantial amount of funds and research resources is being directed into treatment options for these disorders. Naturally, most patients do not usually suffer from a single disease only and can be under treatment for a multitude of disorders. The available studies on drug–microbiome interactions have mostly focused on individual compounds, in order to accurately pinpoint and isolate their effects on microbiota. However, this does not realistically represent the conditions within the average human body, because of the frequently encountered polypharmacy, and there is great paucity on the studies exploring the joint effects of various drugs on the microbiome.

Moving on, directly targeting the microbiome to induce certain benefits to the host organism is a promising idea, with several potential applications. The first example of microbiota-targeted drugs are antibiotics. The classical antibiotics have a widespread effect on gut flora and are not specific against pathogens. The development of species-specific antibiotic compounds is an attractive alternative, but unexpected changes in the rest of the bacterial community may arise (Guo et al. 2015), possibly due to the complex interactions that underline bacterial symbiosis. On the other end of the spectrum, instead of removing pathogens, promoting the growth of beneficial strains with prebiotics still remains relevant in everyday practice, but the scope of these prebiotics is limited (Kuntz and Gilbert 2017). The development of substances that will fine tune the inter-relationships of different xenobiota is thought to provide a more subtle approach to the more aggressive, usual antibiotic or prebiotic substances, and exploit pre-existing pathways between bacteria, for various purposes, or restore balances that have been disturbed during the course of several disorders, autoimmune included (Garber 2015). This option seems to be rather far in the future, however, due to the limited knowledge and available compounds of the sort. Finally, probiotics, the introduction of bacteria in the organism, have been used for decades and are known to confer various benefits. Efforts are being made to isolate bacteria that produce specific compounds, in order to have a particular treatment potential (Kuntz and Gilbert 2017). The fact remains, though, that to successfully introduce these bacteria, numerous factors of the host organism need to be taken into account, such as genetics and nutritional habits, so integrating various ecological interactions will be crucial to the success of targeted probiotics.

Overall, introducing the microbiome into precision medicine faces several challenges. Clinicians have proven reluctant in applying genetic information in everyday practice, despite the available evidence, and so metagenome and personalized microbiome information might also be ignored, despite their significance. Legal hurdles are also present, in both providing and using this sort of personal data and for getting granted the necessary approvals to move forward

with any treatment involving the microbiome, such as fecal transplant (Kuntz and Gilbert 2017), which in turn leads to lack of data regarding their large-scale application.

24.7 Difficulties of Studying Microbial Pathomechanisms in Autoimmune Diseases

Microbial agents are known initiators of autoimmunity via mechanisms including molecular mimicry, immunological cross-reactivity, bystander activation, and epitope spreading (von Herrath et al. 2003). Elegant studies on animal models have exploited the role of viruses such as EBV, CMV, HPV, and HSV in systemic lupus erythematosus, multiple sclerosis, and other organ specific and non-organ specific autoimmune diseases. However, the investigation of pathogen-driven autoimmunity so far has been mainly based on experimental models that imitate the human disease but is difficult to be proven in the human setting. Epidemiological studies may identify microbial triggers of specific autoimmune disease but it is not a direct proof of causality.

Thus, one challenge is to prove the causal link between the pathogen and the pathogen-derived autoimmune disease. The interplay between the immune system and pathogens is complicated. Many bacteria have the ability to deregulate the immune system and cause an aberrant immunological response, but not all of them can lead to the induction of autoimmunity. One well-established example is the rheumatic fever. In this case, molecular mimicry between the protein M of *Streptococcus pyogenes* and the human cardiac myosin leads to the loss of immunologic tolerance and the production of cardiac tissue-specific autoreactive T cells and autoantibodies (Guilherme et al. 2006). However, this "one microbe-one disease" mechanism, as defined by the extended Koch's postulates for autoimmune diseases, is likely the exception rather than the rule in autoimmunity models. Also a specific pathogen, for example, EBV or *Helicobacter pylori* may participate in various autoimmune diseases. Finally, most autoimmune diseases, at least in animal models, can be induced by several infectious triggers, from microbes to viruses, and to parasites. Thus, a specific pathogen may be involved in the pathogenesis of more than one autoimmune diseases and autoimmune diseases may be caused by more than one microbial agent.

Another challenge is to establish a strong temporal link between the microbial agent and the autoimmune disease. The exposure to the microbial agent and the induction of autoreactive T cells and autoantibodies may precede the clinical manifestation of autoimmunity by decades. Thus, to establish such a link is almost impossible to identify in clinical studies. Even the presence of autoantibodies or other autoimmune phenomena in sub-clinical phases or very early stages of the disease may have nothing to do with what has been the impetus (also known as the "original sin") of pathogen-self encounter at "day zero" decades ago. Anti-citrullinated peptide antibodies appear up to 10 years before the onset of clinical arthritis in rheumatoid arthritis and T-cell and antibody epitope specificity in early

stages changes over the time (epitope spreading) (Sakkas and Bogdanos 2016). A pivotal role in the induction of these autoantibodies is played by *Porphyromonas gingivalis*, a commensal bacterium of the oral cavity involved in periodontal disease, because of its ability to cause citrullination of host proteins (Abdullah et al. 2013). Although the exposure to many commensal microbes, including *Porphyromonas gingivalis*, seems to be continuous, it is difficult to investigate the time, the duration, and the extent of this exposure. In addition, it is even more difficult to investigate in vivo how this exposure affects the function of the immune system and to set a limit above, which autoreactivity may be induced and whether this will lead to autoimmunity. Finally, the same commensal bacteria, which are linked with autoimmune disease, such as *Prevotella* spp. in rheumatoid arthritis may prevent from it, or from another disease, for example, multiple sclerosis.

24.8 Concluding Remarks

The complexity of microbiome research has led to several questions that still need definite answers, especially regarding the preclinical research level; Guthrie et al. collected the most crucial of them, shown in Table 24.1 (Guthrie and Kelly 2019). Technical issues and the existence of numerous confounding factors perplex matters even further, while translatability is still a major hurdle. The lack of standardized procedures and differences between studies, for example, in defining populations and handling/analyzing samples, usually disallows the drawing of accurate conclusions (Debelius et al. 2016). In an attempt to help towards research of higher quality and significance, the Microbiology Society's *Unlocking the Microbiome* report has provided a list of recommendations for future research (Marchesi 2018), shortly presented in Table 24.2.

Large-scale studies can provide crucial information on which factors have extended influences on microbiota, but designing and conducting them is not an easy task. In this case, well-designed, smaller-scale studies that focus on answering particular questions in well-defined populations can play an important part in promoting research and adding valuable knowledge to the community. It is

Table 24.1 Unanswered questions for the preclinical research of the microbiome

1. Is an individual's microbiome indicative/predictive of their response to treatment?
2. Which microbiome characteristics carry the biggest predictive value in this sense?
3. What is the temporal perseverance of microbiome phenotypes in patients?
4. What are the impacts of diet and antibiotics on treatment outcomes?
5. What intrinsic factors of the host, implicated in microbiome function, influence response to treatment?

Table 24.2 Abbreviated version of the Microbiology Society's list of recommendations for future research on the human microbiome

Domain	Recommendation
Evidence base creation	Cooperation of researchers and funders, for longitudinal studies with bigger-samples to be conducted, and to reproduce results, identify biomarkers, and assess the influence of various factors to the microbiome
Interdisciplinary research and knowledge exchange	Promotion of community-led cooperative efforts, which shall be multidisciplinary (various scientific fields), cross-cutting (various microbiome model experts), and effective at several levels
Research capacity promotion	Development of early scientific career training and education in areas such as bioinformatics, and organization of workshops, training networks and proper infrastructure for resource acquisition
Data and resource availability	Establishment of global standards for data access and interoperability, and efficient long-term data management, via well-maintained and curated databases
Best practices and standards	Agreement on the standards and best practices by all involved parties
Translatability increase	Promotion of academic-industrial collaborative networks, early collaboration with policy-makers, regulators, and end-users, for the timely development of regulations regarding microbiome products and interventions
Microbiome research and society	Public sensitization towards microbiome research, via cooperation with policy-makers, educators, and press members

recommended that smaller studies concentrate on fulfilling the following four criteria: narrow focus, adequate sample size, minimized technical heterogeneity, and ample metadata collection (Debelius et al. 2016). Limiting the focus will add to the accuracy of the small study, which inherently has smaller power in detecting large-scale, broad effects, and minimizing technical and analytical variations will help in more safely pooling the results of these small studies and meta-analyzing them.

It is encouraging to see that new techniques for the study of microbiota are emerging (Lagier et al. 2016; Zhang et al. 2019), and that many companies are currently developing and testing microbiota-based regimes for several autoimmune and inflammatory disorders (Garber 2015; Thaiss et al. 2016), showing how all the challenges we mentioned in this chapter have not hindered progress and that it is a matter of time before they are overcome. Furthermore, innovative methods with patient samples can be useful in identifying cross-reacting microbial epitopes and novel autoantibodies for the diagnosis of autoimmune disorders (Pianta et al. 2017), while high-throughput microbiome assays can be a viable option in rapidly and efficiently assessing drug–microbe interactions (Zhang et al. 2019). This screening may also assist in pinpointing previously unknown effects of drugs on the microbiota and reveal novel therapeutic potentials for the compounds.

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Future Therapeutic Prospects in Dealing with Autoimmune Diseases: Treatment Based on the Microbiome Model

25

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Abstract

Therapy of autoimmune diseases is subject to change tremendously over the last two decades due to the emergence of biologic and synthetic drugs. In parallel, the detachment of microbiome research from the culture-based methods and the advancement of culture-independent techniques such as whole-genome shotgun metagenomics offered a new perspective to overcome the non-disease specific

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medication to a more personalized microbiome-based treatment. Gut dysbiosis based on numerous studies has been linked to the majority of autoimmune diseases and presumably the microbiome at present accounts for a new field for potential interventions. Several new microbiota-centred approaches, namely faecal microbiota transplantation, probiotics and prebiotics among the most widely known have pros and cons but mostly warrant in-depth elaboration and well-designed clinical trials in order to establish safe and effective therapies. In this chapter we are presenting current knowledge with respect to microbiome, microbiome–immune interactions and linkage to autoimmunity, microbiome-based modifications for restoring homeostasis in autoimmune diseases and challenges and future opportunities towards a more patient-centric treatment in the context of personalized medicine.

Keywords

Autoimmunity · Autoimmune disease · Microbiome · Microbiota · Faecal Microbiota Transplantation (FMT) · Prebiotics · Probiotics · Dysbiosis · Personalized medicine

25.1 Introduction

Autoimmune diseases (AIDs) during the last decades have gained a lot of attention from the scientific society. There are some experts who believe that an 'autoimmune pandemic' is just around the corner. With more than 100 pathological entities for a great number of patients with an aberrant adaptive immune response and the implication of B and T lymphocyte against various self-antigens, it is of paramount significance to create the best strategy to deal with. The probable causes of autoimmunity are not completely clarified. Various factors likely the genetic context of the host in relation to diet, lifestyle, environment and infections in some respects outline the potential pathogenic background (Miller et al. 2012; Ramos-Casals et al. 2015). A plethora of human and animal studies have introduced the unique role of microbiota in the generation of autoimmunity. Microbial composition perturbations may lead to failure of immune tolerance to self-antigens ending to showcase the potential role of microbiome in flaring up the autoreactivity and the subsequent tissue injury and overt AID (Belkaid and Hand 2014; Shamriz et al. 2016).

A collective terminology 'microbiome' represents the numerous microorganisms and their genes dwelling humans since their first appearance on earth. Big data concerning the composition and functionality of these diverse populations have grown out of the unprecedented breakthroughs in the observational ways of scientific research. New technologies, namely next generation sequencing (NGS) offered handy and sophisticated tools to study these unexplored worlds. Large cohort studies lying on the findings of new methods brought light to the role of microbiome with regard to autoimmunity as 'protective, neutral or provocative' (Yurkovetskiy et al. 2015).

In the ever-growing current efforts to treat AID it is now more than obvious that a new field for exploration has emerged and it is the human microbiome of the gut in particular. It seems that the most extreme task is to define the 'healthy gut microbiome' and the causality to AID. It comes as no surprise that treatments targeting intestinal microbiota are very tempting to apply in patients and have gained a lot of attention. Already tested therapies in certain AID like faecal microbiota transplantation (FMT) represent the solid background to expand to new promising boundaries, namely pharmacomicrobiomics and various functional foods. In this chapter, we present gut microbiome as the ultimate therapy target in AID, exploring existing knowledge gaps, breaking down the old-fashioned approaches and finally thinking outside the box in order to elucidate the future perspectives in personalized treatments.

25.2 The Era of Microbiome

25.2.1 The Current Knowledge of the Human Microbiome with the emfasis on the Gut

During the last two decades scientists achieved to partially identify the base of the iceberg in the context of the uncultured microorganisms with the traditional culture-based microbiological techniques. The richness of the microscopy observations considering microbes was not mirroring the results of the microbial cultures until the introduction of new culture-independent technologies and bioinformatics. Next generation sequencing (NGS), 16S ribosomal RNA gene sequencing and especially metagenomic shotgun sequencing have offered new perspectives in the study of microbiome, focusing not only on what is over there but what exactly they are doing. Two ambitious projects the Human Microbiome Project (USA) and the metaHIT Consortium (Europe) managed to characterize the microbial communities in different body sites, all the microorganisms' genes and their interconnection through changes in health and disease (NIH Human Microbiome Project 2020; MetaHIT Consortium 2021; The Human Microbiome Project Consortium 2012).

More than 100 trillion of bacteria, fungi, protozoa and viruses seem to outnumber human cells with a revision of a previous perception from 10 to 1 until 1 to 1, introducing a 'new actor on stage' playing a variety of roles in health and disease (Sender et al. 2016; Tsigalou et al. 2018). Six dominant phyla compose the majority of microbes: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria, Actinobacteria* and *Verrucomicrobia* (Qin et al. 2010). Without any doubt, the gastrointestinal track represents a whole world of microbes with 2172 microbial species with 90% of them to be *Firmicutes* and *Bacteroidetes* (Mahajan et al. 2021; Hugon et al. 2015; Almeida et al. 2019; Forster et al. 2019; Konstantinidis et al. 2020). Data from new methodologies, indicates that due to gut microbiome variations healthy European individuals were classified to three enterotypes (Zoetendal et al. 2008; Segata et al. 2012).

As these microbial societies co-evolved with humans, they polished up the symbiotic interaction with the host. Microbiota offers certain benefits to the host with reward that is to say harvesting energy, synthesis of essential amino acids and vitamins, metabolism regulation, protection from pathogens, maturation and regulation of immune system shaping an intact gut mucosal epithelium, etc. (Mahajan et al. 2021). These functions count toward maintaining homeostasis and securing 'eubiosis' which is essential for the well-being. Any kind of loss of microbial diversity and/or abundancy may lead to 'dysbiosis' when the balance between commensals and pathogens disappears (Fig. 25.1). During dysbiosis the intestinal mucosal barrier loses its integrity and the immune system becomes exposed in microbial products, e.g., LPS leading to endotoxemia, leaky gut syndrome, inflammation and various pathologies (Cani et al. 2007). This condition is related according to human and experimental studies with numerous diseases as obesity, cancer, AID, asthma, diabetes mellitus, autism, etc. (Vallianou et al. 2020a, b, 2021; Castaner et al. 2018; Clemente et al. 2018).

Bacteria are omnipresent in and on the host from the uterus until the end of life (Amenyogbe et al. 2017). A variety of factors affect the development, composition and perturbations of gut microbiota. Among those determinants affecting gut microbiota are the delivery mode (caesarean section or vaginal), gestational age and feeding mode, antibiotic administration in early life, probiotics, prebiotics, alcohol abuse, geography, diet and lifestyle, age, gender, smoking, infections, urban or rural living, vaccinations, stress, genetics, hormones etc. (Thursby and Juge 2017; Yu et al. 2013; Marcobal et al. 2011; Bezirtzoglou et al. 2011; Penders et al. 2006; Favier et al. 2002; Sprockett et al. 2018; Jayasinghe et al. 2016; Mutlu et al. 2012; Tsigalou et al. 2021). The diversity and abundancy amplify from early life to adulthood and then a little at a time deplete (Belizário and Napolitano 2015).

25.2.2 From Eubiosis to Gut Dysbiosis and Inflammation

There is mounting evidence from numerous studies that eubiosis plays a pivotal role in maintaining host's health and preventing disease. The well-balanced microbiome offers a safe environment for development, maturation and healthy aging of human host by affecting or even governing a plethora of functions. Conversely, a disorganized gut microbial community as it is in dysbiosis might be the spark that set the fire of illness or disorder (Méndez-Salazar et al. 2018; Belizário et al. 2018; Brown et al. 2020).

The interaction between commensals and host represents a crucial network influencing the growth and homeostasis of the immune system (Belkaid and Hand 2014; PrabhuDas et al. 2011; Siegrist 2001). Key players in this dialogue are the different types of pattern recognition receptors (PRRs) with members like toll-like receptors TLR, type C-lectine receptors CLR, etc. (Valentini et al. 2014). TLRs bear the duty to recognize either molecular model associated patterns MAMPS from commensals or pathogen-associated molecular patterns from pathobionts (Guven-Maiorov et al. 2017; Kollmann et al. 2012). Additionally, resident

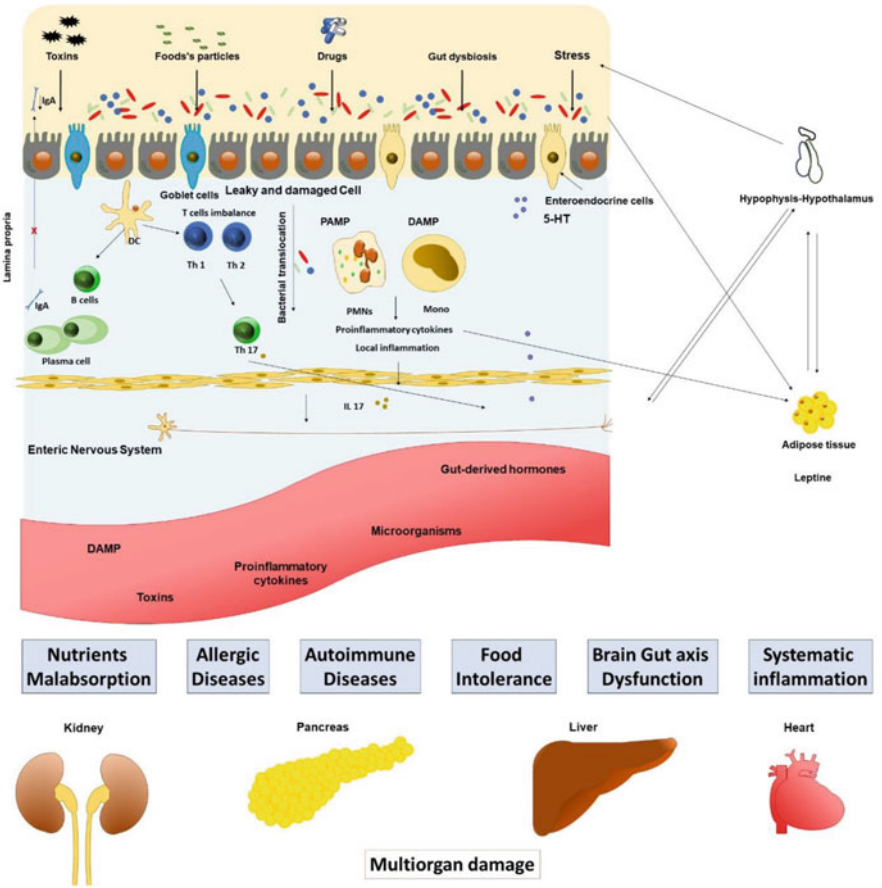

Fig. 25.1 The gut microbiome is affected by environmental exposures such as diet, toxins and antibiotics. Physiologically, mucus produced by the Goblet cells contributes to maintain the inter-species bacterial balance. Gut dysbiosis can alter many basic equilibrium: affects mucus production, trigger the dysfunction of epithelial barrier and enhance intestinal permeability. The hyperpermeability facilitates the translocation into the enterohepatic circulation of viable pathogenic bacteria or/and microbial products lipopolysaccharides (LPS). Moreover, bacterial translocation and local cells damage mediate the activation of immune cells such as PMNs and PBMCs. Activation of host immunity, promoting long-term disease. [*Abbreviations*: *DCs* dendritic cells, *DAMP* damage-associated molecular patterns, *PMNs* polymorphonuclear leukocytes, *PBMCs* peripheral blood mononuclear cells, *PAMP* pathogen-associated molecular patterns, *Th* T helper cells]

microbiota contributes to the development of intestinal lymphoid tissue and the maturation and integrity of gut lumen epithelial cells and gastric mucosa (Hooper et al. 2001; Stappenbeck et al. 2002). It is obvious nowadays that microbiome promotes regulatory immune responses and immune tolerance by modulating the regulatory T reg. Cell function through IL-10 and TGFb. For example, *Bacteroides*

fragilis by producing polysaccharide A promotes IL-10 and limits Th17 immune response during inflammation (Chang et al. 2014). In unison short chain fatty acids (SCFA) have a significant role in health by anti-inflammatory process. They exert the function of Tregs and macrophages hampering local and systemic inflammation (Chang et al. 2014; Furusawa et al. 2013; Shevach 2009). SCFA and mainly butyrate seem to be a weighty factor for the integrity of gut barrier and for immune regulation (Kelly et al. 2015). Decrease of SCFA during dysbiosis may cause inflamm-ageing in the intestinal lumen of the elderly (Chang et al. 2014; Furusawa et al. 2013).

Gastrointestinal microbiota is under the direct impingement of the host immune system. The shaping of multifarious barriers offers protection from injury and promotes the maintenance of a homeostatic niche in the gut (Mahajan et al. 2021). Different enzymes and antimicrobial peptides, secretory IgA, epithelial cells and mucus production in tandem with gut-associated immune tissue and cells protect the host immune system from the overt exposure to microbiota and prevent loss of immune tolerance through 'leaky gut syndrome' (Guilherme et al. 2006). Antimicrobial proteins, namely α-defensins, cathelicidins, collectins, histatins, lysozymes, lectins, etc. eliminate bacteria. Bacteria biofilm produced by secretory IgA together with intestinal microbiome minimizes the exposure of the epithelial interface to pathobionts (Hooper and Macpherson 2010; McGuckin et al. 2011; Rogier et al. 2014). Disbalanced gut microbiome can disturb the intestinal mucosal barrier and create metabolic endotoxemia because of the exposure to different microbial products such as high levels of membrane lipopolysaccharides (LPS) (endotoxin). When endotoxemia is connected to augmented gut permeability might flare up the inflammation process with inflammatory immune cells activation, Th1 Th2 imbalance and high amounts of pro-inflammatory cytokines and chemokines (Vallianou et al. 2021; Cani and Delzenne 2007). Only recently the mechanism of dysbiosis and endotoxemia has been proposed to justify as a potential mechanism, the severity of COVID-19 in obese subjects with chronic low-grade inflammation (Belancic 2020).

25.2.3 The Chicken and Egg Situation-Proof of Causality?

It is well known that gut dysbiosis has a negative impact on various systems' functionality and welfare of the host. Until now scientists have focused on the 'abnormal' shifts of the microbiome with regard to multiple diseases although having in mind that 'normal' and 'abnormal' in the field of microbiome research are not so unambiguous. The intestinal microbiome due to its contribution to body functions seems to be a 'microbial endocrine organ' or an 'active organ' could be 'at the intersection of everything' its alterations are the last decades under the microscope of the broader scientific community in order to establish causality between dysbiosis and pathological conditions (Bezirtzoglou and Stavropoulou 2011; Cani et al. 2007; Clarke et al. 2014).

It is not fully clarified which situation comes first; the alteration of gut microbiome causes the pathological condition or it is merely the consequence of the disease. The question arises is like an ancient causality dilemma of the chicken or

the egg. A bulk of knowledge exists but mostly concerns the interconnection among pathogenesis, symptoms, therapy interventions and prognosis with microbiota alterations, failing to demonstrate conclusively a causative role of these shifts. Being aware that dysbiosis is a critical condition which deprives the GI from the high diversity and abundance of commensals in favour of pathogens. Human and animal studies strived to establish that a dysregulated microbiome might lead to disease and moreover different manipulations might offer prevention, delay, better prognosis or even cure.

The usual finding in the majority of studies is the loss of diversity and richness and lower microbial gene count during the pathological condition failing to highlight the healthy microbial signature for sure. Although there is accumulating evidence that the microbiome dysbiosis is incriminating for a plethora of pathologies there are still controversies and liability issues. The standardization of the protocols of specimen collection and DNA extraction, coupled with the big data analysis through bioinformatics are need to be impruved in order to clarify the causality in microbiome-disease relationship. This will promote for sure the intensification of the intervention prospective studies targeting gut microbiome in various ways exploiting neutraceuticals, FMT, etc.

25.2.4 The Emerging Role of Microbiome in Autoimmune Diseases-Mechanisms and Interactions

The human evolution is closely associated with trillion microorganisms that colonize human body starting from intrauterine development of the foetus. This symbiosis delves deeply during the adult life. A normal microbiome protects the body from pathogens, maintains the integrity of the intestinal wall and supports homeostasis. The connection of the microbiome with the nervous, immune and endocrine systems has not been fully understood. The link between the microbiome and different disorders has previously demonstrated in animal models' as well as human studies (Xu et al. 2021). Microbial dysbiosis leads to the development and/or exacerbations of autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), ankylosing spondylitis (AS), ulcerative colitis (UC), type 1 diabetes (T1D) and more others (Ruff and Kriegel 2015; Valiente et al. 2022; Popov et al. 2021; Han et al. 2018; De Luca and Shoenfeld 2019). Microorganisms can affect inflammation through different mechanisms such as increasing intestinal permeability or leaky gut, molecular mimicry, enzymes production, etc.

25.2.4.1 Microbiome-Immune Axis

Numerous studies have suggested that the interaction between a harmonious ecosystem of human microbiota and the host immune system plays the synergetic roles in maintaining homeostasis (Bose and Mukherjee 2019; Lloyd-Price et al. 2016). The main definition of the gastrointestinal mucosa as "an immune related organ" is the intestinal associated lymphoid tissue Gut-associated lymphoid tissues (GALT), which is defective in mice without germs. Microbial-free mice show fewer Peyer's

plaques and mesenteric lymph nodes of the bowel, compared with animals containing microbiota. In microbial mice, intestinal epithelial cells (IECs), which line the gut and form a physical barrier between the lumen and the immune system, show reduced expression of Toll-like receptors, (TLRs) and the major histocompatibility molecule II (MHC II), which are involved in the perception of pathogens and presentation of antigens, respectively (Round and Mazmanian 2009). Consequently, multiple populations of intestinal immune cells need a microbiota for their development and their function.

The gut microbiota plays an important role in the development of $CD4^+$ T cells (Wu and Wu 2012; PMID: 22356853). The absence of microbiota also leads to several cellular defects, including a decrease in the number of $CD4^+$ T cells in the spleen, a decrease in the number of germinal centres in the spleen and a decrease in the level of systemic antibodies, which indicates that the microbiota can form systemic immunity. Moreover, germ-free mice exhibit defects in the maturation of gut-associated lymphoid tissues and mesenteric lymph nodes, leading to attenuated production of secretory IgA (s-IgA) (Round and Mazmanian 2009).

25.2.4.2 Leaky Gut Syndrome (LGS)

Microbial dysbiosis often leads to enhanced intestinal permeability (Ahmad et al. 2017). This pathological status is named 'leaky gut syndrome' (LGS). LGS initiates inflammatory responses in the intestine and in extraintestinal tissue. Some microorganisms that are often overrepresented in the microbiota of patients with inflammatory disorders are characterized as 'intestinal pathobionts' which accelerate systemic inflammation by translocating across the epithelial barrier to reach extraintestinal tissue. The classical intestinal pathobionts are *Enterococcus gallinarum* and *Proteus mirabilis* (Vieira et al. 2018). Previous studies report that LGS is linked with oral microbiota. The daily use of proton pump inhibitors (PPI) facilitates the translocation of otherwise oral indigenous bacteria to the intestine (Imhann et al. 2016). *Porphyromonas gingivalis*, a periodontopathic bacterium, may predispose hosts to systemic inflammation and autoimmunity. Mukuls et al. report *P. gingivalis* peptidyl arginine deiminase (PPAD) produced by this bacterium, is capable of protein citrullination (Mikuls et al. 2009). Citrullination is one of these modifications, where an arginine amino acid is converted to a citrulline amino acid. It is well known that the autoimmune disorders are able to trigger by citrullination (Alghamdi et al. 2019).

25.2.4.3 Molecular Mimicry

At the end of twentieth century, a new mechanism named 'molecular mimicry' by either a virus or bacteria was proposed to initiate and exacerbate an autoimmune response. Initial work by Fujinami et al. identified mouse antibodies from antibody-secreting B cell clones, which were reactive to both intermediate filaments of normal cells and viral proteins of measles virus and herpes simplex virus (HSV-1) (Fujinami et al. 1983). In addition, the expression of dual TCRs by the same T cell has been proposed to be a potential mechanism for molecular mimicry in autoimmune disease (Blichfeldt et al. 1996). Recently, Rojas et al. have postulated four major criteria that are reasoned to account for molecular mimicry (Rojas et al. 2018):

1. Similarity between a host epitope and an epitope of a microorganism or environmental agent.
2. Detection of antibodies or T cells that cross-react with both epitopes in patients with autoimmune disorders (AIDs).
3. Epidemiological link between exposure to the environmental agent or microbe and development of disease.
4. Reproducibility of autoimmunity in an animal model.

During the last 30 years, the molecular mimicry as a possible mechanism of autoimmune diseases was proposed for ankylosing spondylitis, Guillain–Barré syndrome, SLE, RA and other autoimmune diseases.

25.2.5 Gut Microbiome Alterations in Certain Autoimmune Conditions

The interplay between intestinal microbiome and host immune system proposes that a key player in pathogenesis of AID is the disorganized gut microbiota through the aforementioned mechanisms. Multitudinous studies point out the potential immunomodulating contribution of specific bacteria in AIDs.

Zang et al. have depicted the significance of gut microbiome with Systemic Lupus Erythematosus (SLE) in an experimental model of a lupus-prone mice that was associated with early onset and severe symptoms and the same has been demonstrated in humans as well (Zhang et al. 2014; Hevia et al. 2014; Luo et al. 2018). Moreover, manipulation of intestinal microbiota has an impact on disease activity (Mu et al. 2017; Ma et al. 2019). He et al. proposed the footprint of gut microbiome in SLE patients including microbes such as *Rhodococcus, Eggerthella, Klebsiella* and *Prevotella*, etc. (He et al. 2016).

Dysbiosis is considered among the triggering factors as smoking and infections alongside with HLA genes for autoimmunity in patients with rheumatoid arthritis (RA) (Klareskog et al. 2006; Brusca et al. 2014). In the faeces of RA patients *Prevotella copri* and *Ruminococcus gnavus* thrive (Alpizar-Rodriguez et al. 2019) and an augmentation of *Lactobacillus salivarius* has been associated with more intense disease activity (Zhang et al. 2015; Liu et al. 2013). Chiang et al. in 2019 pointed out that Chinese RA patients anti-citrullinated protein antibody (ACPA) positive had different gut phenotypes compared to ACPA-negative ones including *Blautia*, *Akkermansia* and *Clostridiales* (Chiang et al. 2019).

In Sjogren's Syndrome (SS) patients a growth of *Streptococcus* and *Veillonella* and a reduction in *Synergistetes* and *Spirochaetes* have been monitored (Siddiqui et al. 2016). Apart from reports that mention augmentation of various enteric pathogens comparing to controls, there is a solid case concerning severity of the disease. Specifically, SS subjects with highly disturbed gut microbiome (diminution of *Bifidobacterium* and *Alistipes* genera) were presented with intense symptoms, severe ailment and systemic disease activity (Mandl et al. 2017).

The gut–brain axis is well defined in the pathogenesis of multiple sclerosis, thus cerebrospinal fluid CNS has established a crosstalk with intestinal microbiota (Mahajan et al. 2021). Patients under no treatment presented increase in *Methanobrevibacter smithii* (involved in inflammatory conditions) and lower amounts of *Firmicutes* and *Butyricimonas* (produce butyrate and induce Tregs) (Jhangi et al. 2014; Bang et al. 2014).

Clinical findings correlated to dysbiosis in AIDs need further elaboration in order to link the shifts to certain autoimmune pathologies apart from other entities, having also in mind the inter-subject variation through lifespan and the causal connection between the microbiome and diseases.

25.2.6 From Microbiome to Infectome–Autoinfectome: A New Platform

In 2004 Shoenfeld et al. introduced for the first time the provocative idea that 'autoimmune diseases are infectious until proven otherwise' which was complemented in 2012 with the significance of the infectious environment on top of age, sex and genetics in pathogenesis of AIDs by Smyk et al. (Shoenfeld et al. 2004; Smyk et al. 2012).

The concepts of 'infectome' and 'autoinfectome' derived from multiple line of evidence of autoantibody load of infected patients and the mosaic of autoimmunity establish a new approach (Brickman and Shoenfeld 2001; Asherson et al. 2008; Blank and Gershwin 2008; Shoenfeld et al. 2008; Bogdanos et al. 2013a, b). The autoinfectome includes the subsidiary part of the microbiome composed of the infectious agents linking to the development of autoimmune disease representing the opposite site of the previous concept of a 'single infection causes a single AID' (Bogdanos et al. 2015).

Information from the microbiome coupled with infectious agents especially closely related to AIDs such as Epstein Barr virus, Cytomegalovirus and Hepatitis C virus could elucidate and prove a causative link autoimmunity and infection. As a wealth of data demonstrates that specific infectious agents might firearm autoaggression and autoimmunity, the study of the microbiome and specific commensals is promising for an even protective role against autoimmunity (Bogdanos and Sakkas 2017).

25.3 Dealing with Autoimmune Diseases: Where Are We Standing?

25.3.1 Current 'Old-Fashioned' Therapies

The therapeutic interventions for autoimmune diseases can be categorized into: i) a conservative approach of using disease-modifying antirheumatic drug (DMARD); and ii) use of immunosuppressive or immune-modulation therapy with new biological agents. The choice of therapeutical schemes depends on several factors

such as the stage and severity of diseases, the balance between possible side effects and expected positive results, co-morbidities and personal drug specific intolerance (Abbasi et al. 2019; Davidson and Diamond 2001).

25.3.1.1 Disease-Modifying Antirheumatic Drugs (DMARDs)

Disease-modifying antirheumatic drugs (DMARDs) are a class of drugs indicated for the treatment of autoimmune/auto-inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), familial Mediterranean fever (FMF), systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and Sjogren syndrome (SS). They can also be used in the treatment of some types of cancers. Commonly used conventional DMARDs are methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. Each DMARD has different mechanisms of action that interfere with critical pathways in the inflammatory cascade. Conversely, the most conventional DMARDs have several adverse effects unique to each agent or common for this category.

25.3.1.2 Methotrexate (MTX)

Methotrexate was developed as a folic acid analogue in 1947 and used for cancer therapy (Huennekens 1994). MTX is now a commonly used drug in the treatment of many inflammatory disorders. MTX may be combined with other conventional DMARDs or with a biologic agent. When used for treatment of autoimmune diseases, MTX works to reduce inflammation (Cronstein and Aune 2020). The mechanisms of anti-inflammatory actions of MTX include the inhibition of purine and pyrimidine synthesis, interfere to intracellular signalling through translocation of nuclear factor-κB (NF-κB), or via Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. At the cellular level, MTX reduces neutrophil adhesion and migration, inhibits local IL-1 production, reduces levels of IL-6 and IL-8, suppresses cell-mediated immunity and stimulates adenosine release from fibroblasts (Hider et al. 2007). Common side effects include gastric disorders and liver function problems with elevation of hepatic enzymes can occur, even with low doses. Methotrexate can rarely interfere with the bone marrow's production of blood cells with severe pancytopenia (Tiewsoh et al. 2021). Pancytopenia increases the risk of severe infections. Patients taking MTX should take folic acid or other similar agents such as folic acid to reduce the risk of certain side effects. In addition, regular blood tests are necessary for anyone taking methotrexate.

25.3.1.3 Leflunomide

Leflunomide is an immunomodulatory oral medication, belongs to the non-biological DMARDs class of medications. Mechanism of biological action of leflunomide is based on its active metabolite, a teriflunomide. The teriflunomide inhibits the mitochondrial enzymes (Inderbir et al. 2021). Side effects include rash, temporary hair loss, elevation of liver enzymes and gastrointestinal deduction's symptoms like nausea, diarrhoea and abdominal pain. Arterial hypertension can occur as rarer side effect.

25.3.1.4 Hydroxychloroquine

Hydroxychloroquine (HCQ) originally was developed in 1934 as a treatment for malaria. It can be used for the treatment of rheumatoid arthritis. It is also very frequently used for treatment of other autoimmune diseases such as systemic lupus erythematosus and Still's disease (Papagoras et al. 2017). The main toxicity of hydroxychloroquine is the risk of damage to the retina of the eye (Durán-Carrasco et al. 2021). Moreover, the risk from cardiac injury and arrhythmia is increased during the combination pharmacotherapy hydroxychloroquine (HCQ) and azithromycin (AZM) (Zhu et al. 2022).

25.3.1.5 Biological Therapies

Biologic disease-modifying antirheumatic drugs, also known as 'biologic agents', are new group of drugs that are produced using molecular biology (recombinant DNA) techniques. It is started in the 1990s. This group was called 'Biosimilars'. Biosimilars are biological agents that are highly analogous to their reference products. Up to now, numbers of biological agents such as bevacizumab, etanercept, trastuzumab, adalimumab infliximab, rituximab and others have been used.

Different approaches have been used to modify biological function of cells or single molecules. First group is 'soluble receptor antagonists': These are cross-linked forms of superficial cellular receptors that lack the transmembrane and intracellular space. However, these molecules retain a binding capacity that is comparable to normal length receptors on the membrane surface. The prototype of this class is etanercept, a protein consisting of the p75 TNF receptor (Padda et al. 2022).

The second approach to target cytokine function is to use monoclonal antibodies (MA). MA have a higher affinity for a particular cytokine than a soluble receptor targeting the same molecule. Another approach that indirectly targets cytokines is the use of oral small molecule drugs, produced by traditional manufacturing techniques. The above is designed to inhibit selected cytoplasmic protein tyrosine kinases, such as Janus kinase (JAK), which regulates signaling by membrane cytokine receptors (Jasvinder 2022).

25.3.2 Peaking in the Future of Autoimmune Disorders' Treatment

Breaking down the sophisticated build immune response and misdirected to the host give rise to an array of AIDs. A bulk of knowledge exists concerning genetic, immunological, molecular and clinical aspects towards the understanding of these pathologies but on the flip side triggers and underlying mechanisms remain vague for most of them. With regard to treatment, although the quiver is full of arrows there are still unmet clinical requirements. Generally speaking, immune-modulatory drugs for therapy have a broad spectrum of action without specific disease targeted leading to numerous side effects, namely malignancies and infections. Additionally, the percentage of the treatment efficacy is too low and sometimes absent at all. So it is more than obvious that there is a dire need to breathe new life in this field with new

drugs or repurposing ones. This effort has to be based upon better disease comprehension, personalized approach and the exploitation of new diagnostics and technologies (Fugger et al. 2020).

Aside from nutritional intervention as gluten free diet for celiac disease, synthetic drugs, e.g., JAK inhibitors for RA, etc. and biologic drugs such as anti-TNF, anti-BAFF there are a plethora of efforts under testing in preclinical and clinical trials with focus on the patient's needs and personalized treatment.

These more refined and elegant treatments include preclinical discoveries in cellular therapy (e.g., Bregs, CAR Tregs, etc.), CRISPR editing, metabolic targeting and nutritional intervention (SCFA, bile salts, etc.) and adjunctive therapies for organ protection, e.g., in MS (Fugger et al. 2020). Moreover, several drugs and intervention are already under clinical trials such as tolerogenic DCs, fasting and CD40 binding protein for RA, rapamycin for SLE and FMT for MS (Fugger et al. 2020; Karnell et al. 2019; Jackson and Davidson 2019; Roth et al. 2018; Manguso et al. 2017).

An emerging role in monogenic AIDs therapy belongs to genome editing technologies, e.g., genome-wide association studies (GWASs), whole-exome and genome sequencing studies which confer amongst other clinical utilities, treatment selection and response and discovery of new drugs. HLA genes are the first and well known genetic risk elements for efficacy of biologics (Zeggini et al. 2019).

An increased interest has become apparent during the last decade concerning intervention upon environmental factors such as tobacco smoking, infectious agents, obesity and diet. Deep knowledge about these triggering factors contributes to a more sophisticated approach and patient-centric therapy being incorporated in clinic practice. Diet, dysbacteriosis and autoimmune disease seem to be closely interconnected in different levels and modes according to experimental and human studies that demonstrated links for such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), atopic dermatitis (AD) and multiple sclerosis (MS).

25.3.3 New Target Acquisition: The Microbiome

As commensals of the microbiome have down the pike, its essential role in health and disease became apparent. Consequently, it was inevitable that researchers deal with this wealth of knowledge so as to harness their great force to introduce novel therapeutic factors to treat AIDs. Microbiome-based biotherapies for AIDs include diet modifications, prebiotics and probiotics supplementation, FMT, microbial consortia, engineered microbes and new drugs aiming the microbiome–autoimmunity interface. These methods might shoulder current therapies (e.g., steroids, biologics, etc.) as a coordinated and adjunct treatment still under investigation (Zhang et al. 2020a).

Currently, there is no compelling evidence for any type of diet offering the perfect way to modulate dysbiosis. Fasting-mimicking diet (FMD) is a dietary plan with plant-based components that conserve human organism in a fasting condition. In a

murine model with IBD a 4 days FMD plan culminated in reduced gut inflammation and restoration of intestinal pathology (Mahajan et al. 2021; Rangan et al. 2019).

Prebiotics and postbiotics, however, can restore the disturbed gut microbiome in many AIDs administered alone or in combination with certain dietary plan aiming to augment the beneficial effects, for example, *Lactobacillus casei* in RA models and *Prevotella histicola* in autoimmune arthritis and encephalomyelitis in mice (Kearney et al. 2018; Piñero-Lambea et al. 2015; Allegretti et al. 2019; Kao et al. 2017; Ott et al. 2016). What is more, potentials derive from engineered bacteria implanted exerting advantageous properties for AIDs therapy (Maier et al. 2018).

FMT is an old story for gastroenterologists because of its successful use to tackle recurrent *Clostridium difficile* infection for the past decade (Viaud et al. 2013). Yet the implementation on other AIDs is still under investigation with ongoing clinical studies, for example, in RA and spondylarthritis to evaluate their beneficial results. Different modes of delivery namely through colonoscopy or with an oral capsule have been tested with good results (Dominguez-Bello et al. 2019; Conway and Cohen 2015).

Clearly marked microbial consortia or bioactive compounds from microbes could potentially confer to the restoration of gut microbiome (Viaud et al. 2013). Future studies base on new technologies could help to shed light on relationships of microbiota and various medications such as symbionts and pathobionts metabolize for the ssessment of their treatment effect which is downgraded at this time. Gut microbiome eubiosis is nessesary for treatment stratetgy of many diseases. By way of illustration, the antitumor effect of cyclophosphamide(CYC) is only drastic on eubiosis state of gut, stressing out that the development of new precision medication targeting molecules and pathways demands this as a requirement in clinical practice involved in the microbiota-autoimmunity crosstalk (Viaud et al. 2013; Wang et al. 2014).

Nonetheless, the beneficial effects of all the aforenoted therapeutic applications targeting the microbiome to treat AIDs require more studies and also other factors like sex, geography, age to be taken into account when planning microbiome-based personalized treatment strategies. But if the microbiome actually plays a pivotal role in autoimmunity, it is of paramount importance to elaborate novel treatment ways to make available another option apart from traditional immunosuppressive therapies.

25.4 Microbiota-Based Interventions

Recently, Mangalam et al. in a recent review put forward the potential microbial modulations as therapy to treat autoimmune disorders, divided into two categories: the first includes probiotics and the second they coined the term bacteria for drugs ‘BRUGs’. The latter involves non-threatening bacteria with various numbers during intestinal dysregulation (Mangalam et al. 2021). Furthermore, the other methods not limited to prebiotics and FMT are discussed in below sections (Fig. 25.2).

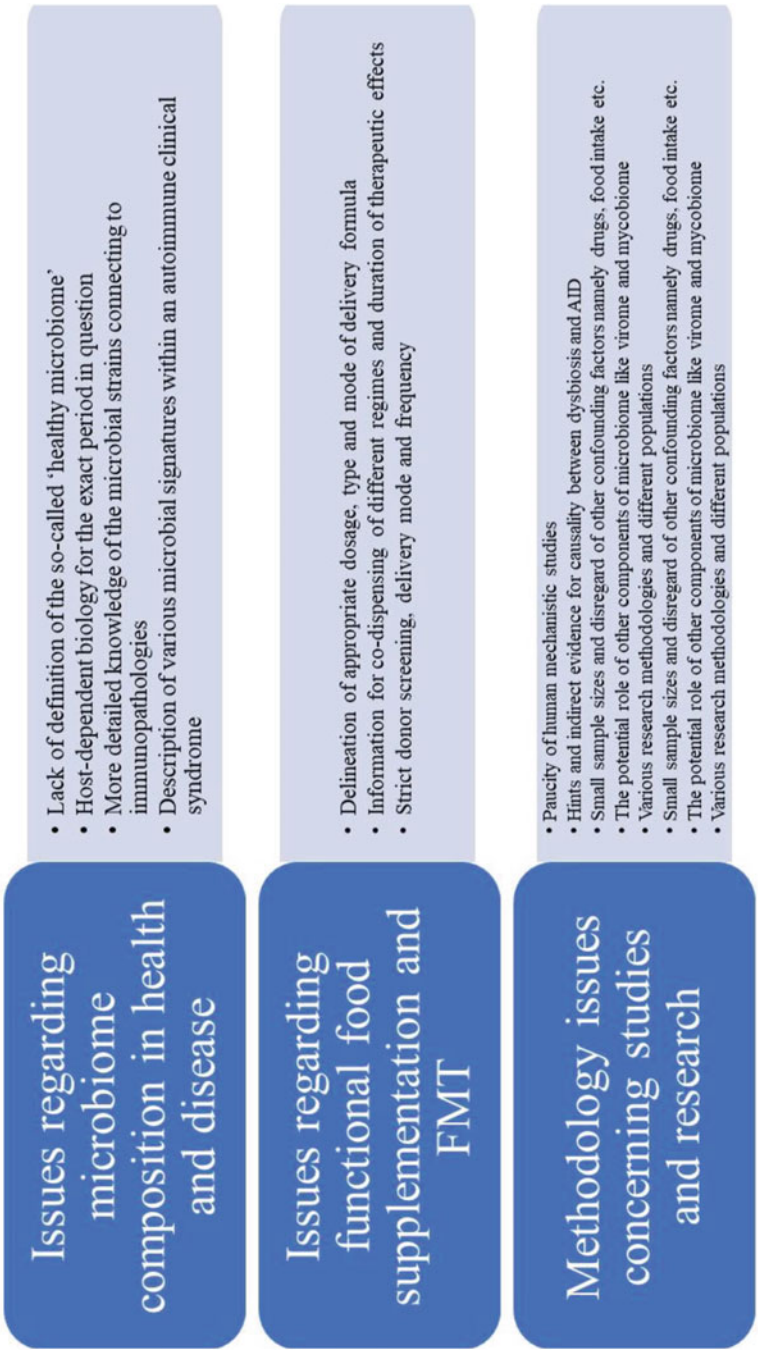

Fig. 25.2 Uncertainties, puzzles and caveats of microbiome-based therapies in autoimmune disorders

25.4.1 Probiotic Applications

The term 'probiotics' first appeared in 1974 and evolved to its present definition as proposed by the Food and Agriculture Organization/World Health Organization in 2002 as 'live microorganisms that confer a health benefit when consumed in adequate amounts' (Hill et al. 2014). There are various ways that probiotics exert their ability to promote microbiome health including mucus and antimicrobial components production, maintenance of gut–epithelial barrier, lowering oxidative stress, effective interactions between mucosal immune cells and intestinal microbial communities and finally intact immune system defence to pathobionts (de Oliveira 2018). Scientists even suggest the potential effect of probiotics for therapeutic approach for COVID-19 (Stavropoulou and Bezirtzoglou 2020). Moreover there are more sophisticated probiotics which have been altered by genetic engineering, e.g., to deliver antimicrobial peptides to kill a pathogen and fight against dysbiosis (Schwartz et al. 2020; Geldart et al. 2015; Sulakvelitze et al. 2001).

Albeit currently probiotics are very popular food supplements globally, evidences for health benefits exist only for antibiotic and Clostridium difficile associated diarrhoea and respiratory infections (Rondanelli et al. 2017). The most broadly used strains in functional foods are *Bifidobacterium* and *Lactobacillus* and also there are next generation probiotics such as *Faecalibacterium prausnitzii, Akkermansia muciniphila* and *Clostridia* strains present in most people's microbiome (Vallianou et al. 2020b). Regrettably the effectiveness of their application in AIDs is still on debate.

In two studies the first from Hatakka et al. and the second from Zamani et al. researchers administered *Lactobacillus rhamnosus* alone or a mixture of *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum*, respectively, to RA patients. Results from the first study were without significant differences apart from 'the feeling better' emotion of the patients in contrast to the second study where they presented refined disease score activity DAS-28 and significant decrease in serum insulin and high-sensitivity CRP (Hatakka et al. 2003; Zamani et al. 2016). Other trials on the effect of probiotics in RA reported not only neutral but even negative results (Mangalam et al. 2021; Liu et al. 2013).

The probiotic administration of different strains (*Bifidobacterium, Lactobacillus, Clostridia, Ruminococcus* and *Synergistetes*) to ameliorate dysbacteriosis in SLE patients induces expansion and differentiation of Tregs and reduces pro-inflammatory cytokines such as IL-6 and TH17 cytokines (Esmaeili et al. 2017).

With respect to MS the gut microbiome is currently recognized as a pivotal player in pathogenesis. In an Iranian study from Kouchaki et al. the use of a probiotic mixture presented a refinement in Expanded Disability Status Scale (EDSS) score and in certain inflammatory biomarkers (Kouchaki et al. 2017).

Novel findings from animal and human studies although in paucity indicate in an inconclusive way the use of probiotics apart from preventive functional food, as an adjuvant therapy of autoimmune disorders. Future clinical trials with better standardization, different probiotic mixture and longer administration might yield to better understanding of their potentials.

25.4.2 The New Concept of BRUGs

Mangalam et al. argue that mono-colonization with the usage of a specific bacterium as part of personalized strategy can be designed for patients with AIDs and will be more effective than a non-specific symbiotics (Mangalam et al. 2021). As personalized medicine is the opposite of 'one size fits all' probiotic administration, animal studies with *Prevotella* spp. and *Bacteroides fragilis* provide evidence of potential therapy.

Prevotella spp. such as *P. histicola* from human subjects contains disease in an experimental model of MS (Chen et al. 2016; Mangalam et al. 2017; Shahi et al. 2019). Another candidate is *Bacteroides fragilis* which has suppressed disease manifestations in animal models of various AIDs such as MS and colitis. Moreover, it presents immunomodulatory properties dependent on bacterial polysaccharide PSA and prevents colonization of pathobionts (Ochoa-Repáraz et al. 2010; Mazmanian et al. 2008).

25.4.3 Prebiotics and Diet: 'Let Food be Thy Medicine and Let Medicine be Thy Food' (Hippocrates 400 BC)

Another strategy to modulate the microbiome is by introducing prebiotics as food supplements. Prebiotics are defined as diet ingredients (non-viable) that are selectively utilized by host microorganisms altering the gut microbial communities conferring beneficial effects for health (Gibson et al. 2017). Mostly studied prebiotics belong to inulin-type fructans ITF and galactooligosacharides (GOS) as stimulatory agents for *Bifidobacteria* and *Lactobacilli* growth to improve intestinal microbiota composition (Hill et al. 2014).

Several studies have focused on the results from functional food application in AIDs regarding Tregs, a very significant population for the induction of autoimmunity. The increase in activity and numbers of Tregs after the administration of probiotics, prebiotics and their metabolites seem to restore immune homeostasis in inflammatory disease and several AIDs, i.e., dermatomyositis, SLE or vitiligo by decrease of inflammatory factors, augmentation of anti-inflammatory biomarkers, diminution of cytotoxicity, etc. (Tsigalou et al. 2018; Antiga et al. 2010; Miyara et al. 2005; Dwivedi et al. 2015; Konieczna et al. 2012).

Apart from probiotics an indirect way to alter microbiome is through diet. 'Let thy food be thy medicine and medicine be thy food', said Hippocrates (400 BC), to emphasize the significance of nutrition generally either for prevention or cure. Few studies have yet elaborated the significance of the diet impact on intestinal microbiota more than genetics. The anti-inflammatory diet in rheumatoid arthritis as well as the Mediterranean diet demonstrated beneficial effects with a decrease of the disease activity in SLE as well (Tsigalou et al. 2020a). Fasting diet and weight loss have improved the disease outcomes in Psoriatic arthritis (Chehade et al. 2019; Winkvist et al. 2018; Forsyth et al. 2018; Claflin et al. 2018; Dahan et al. 2017; Esposito et al. 2018; Yadav et al. 2016; Vieira et al. 2014). Also, the high salt diet is

critical for gut dysbiosis in autoimmune disorders and by reducing salt intake causing increase of SCFA circulation might be a new therapeutic target for SLE (Chen et al. 2020). As celiac disease CD has been connected to SLE, gluten free diet with deprivation of gluten may contribute to ameliorate gut barrier function in SLE (Ludvigsson et al. 2012; Dahan et al. 2016). Taken together the exact role of different diet interventions should be the aim of future studies on recovery of the dysbiotic microbiome during AIDs.

25.4.4 Bacteria Used as Drug-Engineered Microbes: Pharmacomicrobiomics

A large number of patients that suffered from variety of diseases do not response to common drugs for the treatment. Moreover, in many individuals some adverse drug reactions (ADRs) occur after drug administration. To explain the response rate, as well as the possibility of adverse drug reactions, pharmacogenetics and pharmacogenomics technics have been developed. Unfortunately, genetic factors could not explain 100% this phenomenon. In twenty-first century, the gut microbiota has emerged as an important player with pivotal role in many pathophysiological processes. Various studies in animal and humans' models have shown the effect of drug intake on the gut microbiome (Forslund et al. 2015; Devkota 2016). Moreover, an individual's response to a specific drug such as immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis can be attributed to gut microbiome composition (Routy et al. 2018). Recently, the emerging field of pharmacogenetics, which investigates the effect of variations within the human gut microbiome on drugs, has developed. This field was named 'pharmacomicrobiomics' (Scher and Schett 2021; Chen et al. 2022). The gut microbiota as the part of intestinal tract has an impact to absorption ability after oral administration. In vivo studies show that some drugs such as MTX have limited bioavailability (Yan et al. 2021).

25.4.5 Faecal Microbiota Transplantation: A Superior Option?

By the term faecal microbiota transplantation FMT scientists describe the transportation of faeces containing numerous bacteria from healthy donors to patient's intestinal tract aiming to restore eubiosis and to treat various pathologies (Zeng et al. 2019; Pan et al. 2021). It is known since the fourth century in China by Ge Hong where a human faecal suspension was administered orally to a patient suffering from diarrhoea or food poising (Gupta et al. 2020; Zhang et al. 2012). Even from 2013 FMT has been included in the official therapeutic guidelines for the treatment of the *Clostridium difficile* infection (Surawicz et al. 2013) and was successfully tackled the recurrent infections but not limited to it. It seems that it has advantages and there is a growing interest for other disorders, namely inflammatory bowel syndrome (IBS), SLE, etc., but even in a completely irrelevant field as a newly emerged candidate for the elimination of multi-drug-resistant strains (gut resistome) and restoring eubiosis and resilience (Tsigalou et al. 2020b).

There are several acceptable routes for administration apart from colonoscopy such as oral capsule, nasogastric, nasojejunal and sterile faecal filtrates have been applied with satisfactory results (Bafeta et al. 2017; Kao et al. 2017; Ott et al. 2016). Recently knowledge from SLE animal studies has revealed that FMT is effective for their treatment. Animal models of lupus showed that FMT application decreases disease severity, progression and treatment in MRL/lpr mice. In this study there is a question mark about the interaction with the efficacy glucocorticoids (prednisone) and should be cautiously considered (Zhang et al. 2020b). In another more recent study Wang et al. transplanted faecal microbes from mice treated with prednisone to untreated SLE MRL/lpr mice demonstrated lupus lessened without the previous side effects (Wang et al. 2021). Other efforts have been contacted with regard to FMT showing remission in ulcer colitis and halting progression in human new onset type I diabetes with some promising results but surely need further investigation (Moayyedi et al. 2015; de Groot et al. 2021).

As FMT represents a rather invasive strategy with the benefit of the direct modification of the gut microbial communities in favour of homeostasis, there is still lack of convincing evidence in rheumatic diseases. There are a few ongoing clinical trials for type 1 diabetes, multiple sclerosis, RA, ankylosing spondylitis, etc. and also some have been already terminated with no results.

Presumably, there are limitations and disadvantages even though the widespread use of FMT. Ongoing research report that fresh and frozen stool is superior to lyophilized. Moreover, therapeutical manitulations that affects gut microbiome of upper gastrointestinal paths are less effective than lower, whilst one time enema is less efficacious than colonoscopy (Tariq et al. 2019; Quraishi et al. 2017; Jiang et al. 2017; Lee et al. 2016; Furuya-Kanamori et al. 2017; Saha and Khanna 2018). Yet, still we do not know indubitably the best way of delivery mode or the frequency of the FMT application for optimal results in attenuation of autoimmune disease severity. There is a disbelief about previous success in inflammatory bowel disease that may be a result from 'super donor's' faeces with excellent results (Manasson et al. 2020). Safety is another issue that is required and extensive donor screening has to be improved in order to avoid transmission of drug-resistant microorganisms, as it happened with an E.coli strain, from the donor to the recipient (De Filipp et al. 2019; Blaser 2019). The potential pathogenic load of the donor's faeces is suspicious for undesired adverse consequences even spark autoreactivity in predisposed AID patients.

Another contribution of FMT in AIDs treatment is that could augment the expression of intestinal epithelial cells IECs autophagy-related proteins and decrease gut permeability, alleviate intestinal injury in animal models (Cheng et al. 2018). As autophagy is an imperative key factor for gut homeostasis and gut barrier functionality, FMT may also affect some drugs functionality such as rapamycin, regulating autophagy mediated inflammation (Fan et al. 2020, 2021; Zha et al. 2020; Pan et al. 2021; Xu et al. 2020b). Last but not least extracellular vesicle-derived miRNA therapy may apply in SLE by modulating intestinal microbiome. Food derived miRNAs can alleviate colitis and reduce pro-inflammatory factors after transplantation from wild type mice (Liu et al. 2016; Gu et al. 2021; Teng et al. 2018; Diez-

Sainz et al. 2021). EV-derived miRNAs and IECs autophagy confer in restoring the gut balance and adequate barrier integrity by that means preventing autoimmune related gut inflammation.

Additionally, in microbiome-based therapies, the utilization of mesenchymal stem cells (MSCs) alone or concurrently with FMT could be included. Focused therapeutic used for MSCs is based on MSCs–gut bacteria interactions for the repair of gut microbiome and robust immunomodulatory properties. Possessing robust immunomodulatory properties, MSCs could be useful for AID treatment such as SLE (Ding et al. 2011; Naji et al. 2019; Yuan et al. 2016; Wang et al. 2018), IBD (Soontararak et al. 2018; Xu et al. 2020a) and RA (Li et al. 2020) mainly lied on the findings from experimental mouse models. Joined FMT-MSC transplantation methodologies according to Ocansey's opinion would result in improved ratio of clinical remission for IBD patients and a better treatment efficacy for SLE subjects, in contrast to the FMT or MSC transplantation alone (Ocansey et al. 2019; Pan et al. 2021).

Overall, FMT could be a superior choice for supplementary treatment for AIDs due to simplicity in procedure and rather safe administration. Unfortunately, many factors such as the lack of standardization, the variable impact, the quality of the faecal donation comprises obstacles to overcome by future research.

25.5 Conclusions

The ongoing interest for human microbiota, as the 'holy grail' with miraculous capabilities guaranties that deep knowledge of the host–microbiome interactions is probably just around the corner (Fig. 25.3). The integration of experimental, computational and statistical methods for the validation and standardization of all the microbiome-derived data and microbiome-based manipulations may improve our understanding aiming to level up the AIDs therapy choices and future perspectives. Targeting mainly intestinal bacteria could be a great leap forward for the exclusive or adjunct therapies of autoimmune disorders. The whole exosome including microbiome, virome, mycobiome and protozon has gained attention and undoubtfully will offer information for the microbiota-related therapies establishing novel strategies. As up to now, there is a paucity in experimental and human studies concerning microbiome as a new acquisition target with inconclusive and sometimes contradictory results and no proof of causality contributing to AIDs therapy so more detailed trials are warranted. Microbiome-centred treatment strategies exploiting functional foods, diet interventions, FMT and other more sophisticated methods like pharmacobiomics would give prominence and tangible value to the outcome of more personalized solutions as the ultimate weapon to suppress the multifaceted autoimmunity in the foreseeable future.

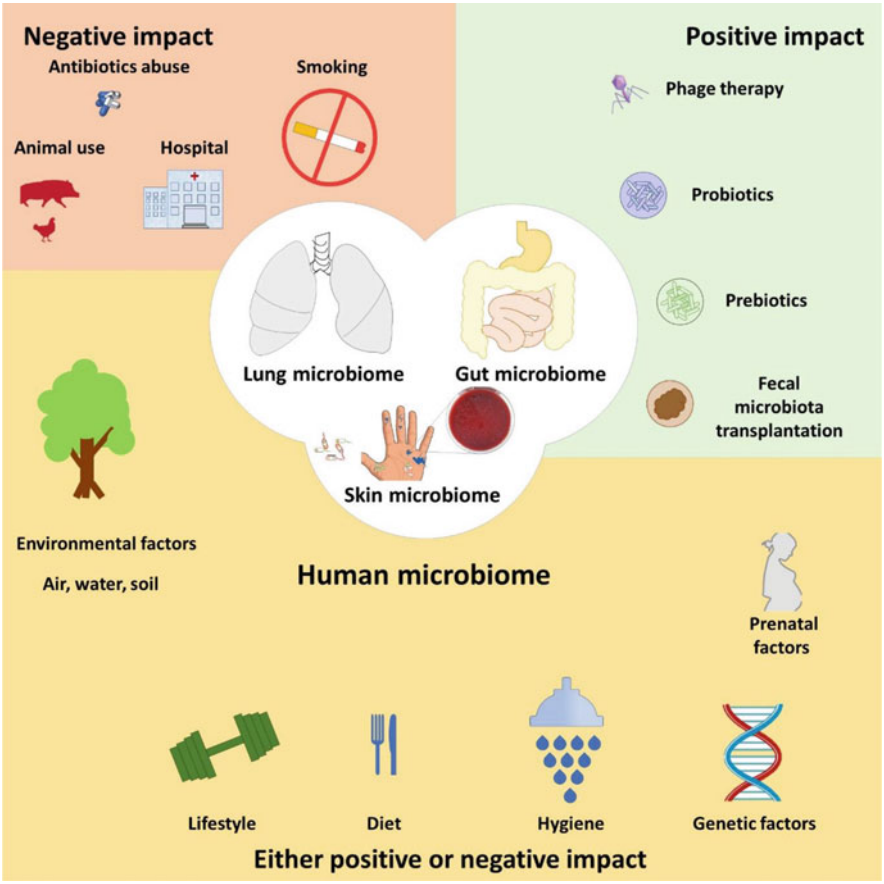

Fig. 25.3 Environmental factors, genetics and microbiome-based interventions and their impact on the human microbiome

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