Diversity and Dynamics of the Gut Microbiome and Immune Cells

4

Prerna Pathak

Abstract

Human microbiome consists of multiple species out of which most of them reside in gut. Gut microbiota is most complex and dynamic in terms of species diversity and therefore regulates the host homeostasis. The intricate relation between the gut microbiota and host is crucial for host functioning. Dysbiosis in microbiota affects myriads of processes which result in multiple diseases such as IBD, type 1 diabetes, and rheumatoid arthritis, etc. This chapter highlights the role of gut microbiota in innate and adaptive immune system development and further explains how alteration in microbiota leads to dysbiosis which makes host susceptible to several diseases.

Keywords

Gut microbiota · Autoimmunity · Innate immunity · Adaptive immunity · T1DM · Rheumatoid arthritis · Systemic lupus erythematosus

4.1 Introduction to Gut Microbiota

Microorganisms are the part of normal human microbiota, over the period of time a symbiotic relationship leads to their colonization in the nasal tract, oral cavity, skin, respiratory, and genitourinary tract (Opazo et al. 2018). Apart from microorganisms, human microbiota comprises protozoans, fungi, archaea as well as viruses (Neish 2009; Sekirov et al. 2010; Sonnenburg and Bäckhed 2016), this collective colonization is termed as gut microbiota. The gastro intestinal tract (GIT) of humans is an intricate open system which harbors 10^{14} microorganisms (Seksik and Landman

P. Pathak (✉)
Jawaharlal Nehru University, New Delhi, India

P. V. Bramhachari (ed.), *Microbiome in Human Health and Disease*,
https://doi.org/10.1007/978-981-16-3156-6_4

2015). Recent advances in deep sequencing technology bring insight about the genome of gut microbiome, it encodes 3.3 billion genes; this surpasses the number of human gene by 100-fold (Dwivedi et al. 2017), therefore it is also termed as "human second genome" (Xu et al. 2019). Human health is governed by the microbes in the gut microbiota which have both favorable as well as pathogenic effects. GIT is the largest region which gets exposed with the external habitat and comprises two-third of the total human microbiome (Virili et al. 2018).

The diversity and the dynamics of the gut microbiota are governed by several factors like age, gender, health alignments, immunity, genetics of the host, geographical changes, lifestyle, and treatments (Ardissone et al. 2014; De Martino et al. 2004). Metagenomics study reveals that the most of the species of the microbiome are missing in the same person at a same time frame; however, microbiota of healthy individuals shows abundant of some species over others (Human Microbiome Project Consortium 2012; Qin et al. 2010). In fact, there is diversity in the microbiota of the gut on the bases of the types of cells; cells of mucus layer, intestinal lumen, and epithelial cells show diverse microhabitats (Sekirov et al. 2010).

Development of human microbiome starts even before the birth as it is revealed by the study on microbiome composition of the placenta (Aagaard et al. 2014). Moreover the study performed on the first stool of the infants shows the presence of 30 genera which are normal inhabitant of amniotic fluid, oral, and vaginal cavity (Ardissone et al. 2014; Clemente et al. 2012; De Martino et al. 2004). It is believed that this is occurred due to mother to child transmission at the time of pregnancy (Lagier et al. 2012). The microbiota of the infants depends on the mode of delivery such as caesarean section born infants have microbiota similar to that of skin while vaginally born infants have vaginal microbiota (Dominguez-Bello et al. 2010). Pregnancy period and the initial few months after the delivery are crucial for the development of the microbiota which further influences immune homeostasis (Gordon Jeffrey et al. 2012).

Breast feeding is another decisive factor that links with microbiome and immunity development (Stewart et al. 2018). Human milk contains ~10^9 bacterial cells/L (Endesfelder et al. 2014), apart from its nutritional value it possesses various bioactive and immunological molecules which govern the microbiome and intestine maturation of the infants. Studies illustrate that immunological components of the human milk such as sIgA, lysozyme, complex lipids, alpha lactalbumin, and lactoferrin impart protection to the infants (Gordon Jeffrey et al. 2012). Initiation and development of microbiota during infant stage impact the health and immunity during adulthood (Ranucci et al. 2017), any perturbation in this development may lead to negative consequences (Fulde et al. 2018). The gut microbiome keeps on evolving from infants to early childhood in a phased manner (Xu et al. 2019).

The mutual relationship between host and gut microbiota plays significant beneficial role. It impacts the development of the gut by influencing proliferation of epithelial cells and host cells apoptosis. Short-chain fatty acids which are the by-product of polysaccharide fermentation mediate interactions between host cells and gut microbiota (Lazar et al. 2018). Apart from maintaining gastrointestinal homeostasis, gut microbiota play role in the development of components of immune

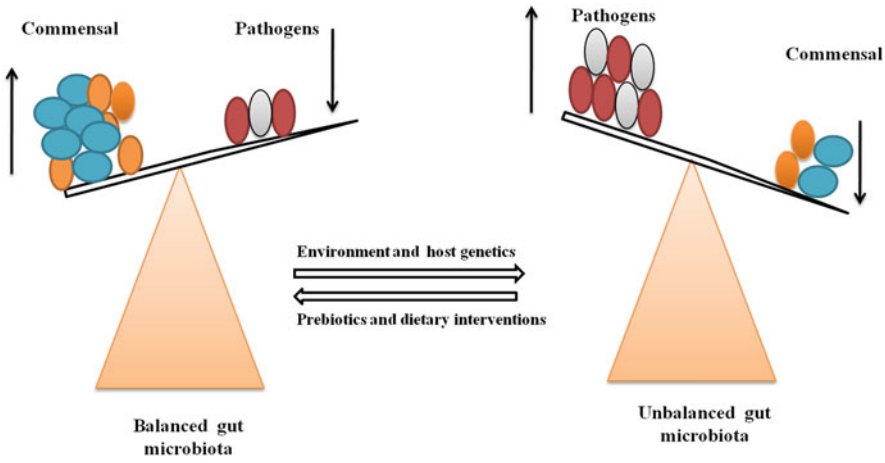

Fig. 4.1 Gut microbiota in normal and diseased conditions

system, synthesis of vitamins like B-complex, folic and biotin, detoxification of xenobiotic compounds, maintaining nutritional homeostasis (Gérard 2013). Among all the known members of gut microbiota, bacteria are most explored. They are classified into three categories, aerobic, facultative anaerobic, and obligate anaerobic bacteria out of which obligate anaerobic dominates them all (Fig. 4.1).

The interspecies balance is pivotal for the proper functioning of the body; this balance is termed as eubiosis. Any imbalance to eubiosis is termed as dysbiosis could lead to plethora of diseases which further affects multiple organs (Clemente et al. 2012). Hereafter this chapter will focus on the role of gut microbiota in the development of immune system and disease.

4.2 Interactions Between Gut Microbiota and Immune System

The symbiotic relationship between the microbiome and the human gut is beneficial for both of them as human gut acts as nutrient source as well as provides breeding habitat to microflora; in return gut micobiota helps in vitamin synthesis, gut development, and forms mucosal barrier as a defense mechanism (Berg et al. 2015). The human mucosa is the largest and the most exposed component to the external environment. Eubiosis is pivotal for maintaining host homeostasis and its defense. The relevance of gut microbiota came into light after the studies performed on germ-free (GF) mice revealed that it produces relatively reduced amount of Intraepithelial lymphocytes (IELs) (Bandeira et al. 1990), IgA-secreting plasma cells (Crabbé et al. 1968), Tregs cells (Ostman et al. 2006), and Angiogenin-4 (Ang4) (Hooper et al. 2003).

Moreover in GF mice, the germinal center of Peyer's patches is smaller compare to conventional mice (McDermott and Huffnagle 2014). Another study illustrates

that concentration of IgA in the feces enhanced reasonably after prebiotics treatment; however, expression of Peyer's patches and pro-inflammatory factor of mesenteric lymph nodes reduced considerably (Carasi et al. 2015). All together these results pinpoint the role of gut microbiota in immunity development as well as eubiosis.

Immune system works basically by recognizing and eliminating the pathogen from our system. The intestinal immune homeostasis is crucial for both host as well as trillions of microbes within the system. This immune homeostasis is a combined effect of innate and adaptive immunity. Several innate and adaptive responses which are crucial in shaping the intestinal microbiota are explained in next section.

4.3 Innate Immunity and Gut Microbiota

Gut-Associated Lymphoid Tissues (GALTs) are present throughout the intestine; they are part of mucosa-associated lymphoid tissues (MALTs) (Brandtzaeg et al. 2008). The innate immune cells of the GALTs are involved in presenting antigen to activate adaptive immune response after recognizing pathogens in a nonspecific manner (Jiao et al. 2020). GALTs have dual function of immune tolerance and immune homeostasis. GALTs include following components; Peyer's patches, isolated lymphoid follicles (ILFs), crypt patches, M cells, appendix, and mesenteric lymph nodes (mLNs) (Brandtzaeg et al. 2008; Mowat 2003). M cells are involved in delivering intestinal antigen to GALTs (Mabbott et al. 2013). Several studies pin point the role of gut microbiota in shaping GALTs. Lymphoid tissue inducer (LTi) cells are involved in formation of secondary lymphoid organs of gut such as Peyer's patches, mLNs, and ILFs (Adachi et al. 1997; Mebius et al. 1997).

Pattern-recognition receptors (PRRs) are crucial for innate immune response; they sense pathogen through specific structures. The pathogen-associated molecular patterns (PAMPs) of the intestinal microorganisms are recognized by PRRs and lead to the development of ILFs. Mouse deficient in PRRs shows defects in ILFs development. PRRs are of several types depending on their location, ligand specificity, and functions, several PRR-related molecules are involved in mechanism like toll-like receptors 2 (TLR2) (Round et al. 2011), myeloid differentiation primary response 88 protein (MyD88) (Medzhitov et al. 1998; Wesche et al. 1997), nucleotide-binding oligomerization domain 1/2 (NOD 1/2) (Bouskra et al. 2008; Clarke et al. 2010; Petnicki-Ocwieja et al. 2009), and TIR domain-containing adaptor protein inducing interferon-β (TRIF) (Bouskra et al. 2008). PRR-PAMP recognition plays pivotal role during host defense response as well as structural development of GALTs.

Toll-like receptors (TLRs) are another crucial member of innate immune system, they recognize specific region in pathogens and start immune response (Rakoff-Nahoum et al. 2004). They are also involved in balancing microbiota composition (Larsson et al. 2012; Wen et al. 2008). Several studies report that TLR5-deficient mice show compositional changes in microbiota (Vijay-Kumar et al. 2010). These changes may further lead to the development of spontaneous colitis, metabolic syndrome, and obesity; this highlights the role of TLR5 in maintaining gut

microbiota composition (Carvalho et al. 2012; Chassaing et al. 2014; Chassaing et al. 2014; Vijay-Kumar et al. 2010).

The nucleotide-binding oligomerization domain-like receptors or Nod-like receptors (NLRs) are intracellular stress sensors of pathogen-associated molecular patterns (PAMPs) associated with cellular stress. Like TLRs, they are also involved in maintaining microbiota composition as it is shown by the study where NOD1/2-deficient mice show altered composition of microbiota (Bouskra et al. 2008; Couturier-Maillard et al. 2013; Petnicki-Ocwieja et al. 2009). Paneth cells which are present in small intestine have enhanced expression of NOD2 protein; upon getting exposed to pathogens this protein induces multiple responses which include cytokines production, autophagy initiation, generation of antimicrobial peptides, and intracellular vesicle trafficking, thus impacts the composition of the microbiota (Couturier-Maillard et al. 2013; Nigro et al. 2014; Ramanan et al. 2014). These members of NLR family elicit immune response after recognizing bacterial peptidoglycans, viruses, and parasites.

Innate immune system functions by initiating response upon sensing the metabolic state of the gut microbiota. Evidence from all the studies reveals the role of innate immune system in governing composition of microbiota (Levy et al. 2015), as mice deficient in *NOD2* (Couturier-Maillard et al. 2013; Petnicki-Ocwieja et al. 2009; Ramanan et al. 2014), *NLRP6* (Elinav et al. 2011), and *TLR5* (Vijay-Kumar et al. 2010), leads to dysbiosis. It is therefore believed that sensors of innate immune system work by promoting the growth of beneficial microorganisms as well as maintaining the stable microbiota. Additionally, there are several other molecules which are involved in maintaining composition of microbiota such as any alterations in paneth cells, which produce antimicrobial peptides (AMPs) lead to dysbiosis (Salzman et al. 2010; Salzman and Bevins 2013). Moreover altered AMP expression brings about alterations in spatial organization of microbiota; RegIIIγ deficiency causes colonization of microorganism in the inner mucus layer, which is devoid of microorganism in normal condition (Vaishnava et al. 2011).

4.4 Adaptive Immunity and Gut Microbiota.

4.4.1 T cells

T cells are the crucial member of adaptive immune system; they are of two types $CD4^+$ T cells and $CD8^+$ T cells. $CD4^+$ T cells are present in lamina propria of intestine and upon activation it differentiates into following subtypes T helper 1 (Th1), Th2, Th17, or regulatory T cell (Treg). The balanced expression of these subtypes is important determinant factor of human health. Each subtype has different functions like Th1 cells play important role during host defense against microorganism, while Th2 cells remove parasitic infections (Wu and Eric 2012). Unregulated Th responses lead to autoimmune diseases and allergic reactions. $CD8^+$ T cells are present in intraepithelial compartment of the gut. GF mice show less number of $CD8^+$ T cells with reduction in their cytotoxicity indicates the role of microbiota in

monitoring $CD8^+$ T cells and its function (Helgeland et al. 2004; Imaoka et al. 1996; Kawaguchi-Miyashita et al. 1996).

Several studies revealed that mice deficient in adaptive immune system display changes in their microbiota, this suggest the role of adaptive immune system in balancing microbiota composition (Kato et al. 2014; Zhang et al. 2015). Mice lacking T cells also show altered microbiota, it is believed that T cells regulate microbiota by triggering expression of AMP; however, there is no direct evidence to this. Rather the prime mechanism by which T cells regulate microbiota is by influencing B cells to produce secretory IgA (Kato et al. 2014). Tregs and Th17 cells are known to be involved in intestinal IgA production, there are reports which suggest that Tregs assist B cells in IgA production (Tsuji et al. 2009). Another study points out the role of Th17 cells in antigen-specific IgA production upon immunization with cholera toxin (Hirota et al. 2013). All together these studies brought insight about the role of T cells in development of microbiota.

4.4.2 B Cells

Another crucial molecule of adaptive immune system which governs the composition of intestinal microbiota is immunoglobulin A (IgA). It is produced by plasma cells into the intestinal lumen where it attaches to microbes as well as microbial components. This generates a physical barrier which averts detrimental interactions with immune system (Pabst 2012). IgA maintains the eubiosis by two proposed mechanism, first by inhibiting the growth or inflammatory effects of microorganisms and secondly by preserving the diversity of healthy microbiota (Palm et al. 2015). Mice deficient in Activation-Induced Cytidine Deaminase (AID) show defect in class switching or somatic hypermutation, this defect is reversed by substituting IgA; this highlights the role of IgA in forging microbiota (Fagarasan et al. 2002; Suzuki et al. 2004), IgA known to play crucial part in forging microbiota during development, as its deficiency fails to curb proteobacteria during microbiota maturation (Mirpuri et al. 2014). IgA is also known to suppress the inflammatory response there by promoting the mutualism between host and microbiota (Peterson et al. 2007). The phenomenon of immune exclusion is mainly involved in suppressing inflammatory response by prohibiting microorganisms from approaching mucosal epithelium (Corthésy 2013). Moreover alternate mechanism by which IgA directly suppresses inflammatory responses is by coating microorganisms gene expression (Cullender et al. 2013). Studies are still at their infancy about how IgA arbitrates these responses.

4.5 Role of Gut Microbiota in Disease Development

The impact of gut microbiota on innate and adaptive immune system is already discussed above, any dysbiosis in microbiota leads to critical diseases. The modification in the eubiotic state of microbiota triggers myriad of diseases such as type I

diabetes, nonalcoholic fatty liver disease, rheumatoid arthritis, obesity, cancer, etc., however how these alterations cause these diseases is still ambiguous. The symbiosis between host and microbiota is crucial for homeostasis. Together, this chapter reveals the crosstalk between host, microbiota, and environmental cues which leads to these pathophysiologies.

4.6 Type 1 Diabetes

Type 1 diabetes (T1DM) was previously called as juvenile-onset diabetes; it is a chronic disease which is linked with high mortality at premature stage (Lazar et al. 2018). It is occurred due to inability of pancreatic β cells to produce insulin due to autoimmune obliteration (Aathira and Jain 2014). Normally this disease occurs during early stage of life but there are reports which reveal that 50% of T1DM occurs in individuals older than 20 year. Several factors govern the development of this disease such as diet, genetics, and gut microbiota (Pociot and Lernmark 2016; Rewers and Ludvigsson 2016; Todd et al. 2007). Data from various studies show that the composition of gut microbiota varies between healthy individuals and individuals with T1DM. Bio-Breeding (BB) rat and nonobese diabetic (NOD) mouse bear alike attribute with that of human disease (Pearson et al. 2016). The composition of gut microbiota in Bio-Breeding diabetes-prone (BB-DP) rats is altered strikingly before and after the outbreak of T1DM (Brugman et al. 2006). Consistent with this, the composition of gut microbiota is altered between healthy and T1DM individuals (Han et al. 2018).

Large amount of research in this direction highlights the role of gut microbiota in TIDM development by regulating immune responses. The outer membrane component of gram-negative bacteria lipopolysaccharide (LPS) or endotoxin is crucial in enhancing the proinflammatory cytokines and damaging the function of pancreatic β cells (Allin et al. 2015), which further leads to diabetes (Pussinen et al. 2011). Another study showed that circulating LPS is higher in T1DM individuals compared to that of healthy individuals (Devaraj et al. 2009). Additionally it is considered that LPS is derived from gut microbiota. Therefore, it is considered as a link between gut microbiota and TIDM (Han et al. 2018). Any change in gut microbiota causes LPS and fatty acids leakage by damaging the mucosal barrier, this leads to simultaneous induction of *TLR4* which results in metabolic inflammation (Velloso et al. 2015). Studies performed in NOD mouse lacking *TLR4* show the increased rate of T1DM development (Gülden et al. 2013). Moreover, a study in NOD mice lacking MyD88 reveals that the T1DM development is not their when raised under specific-pathogen-free (SPF) condition; however, NOD mice lacking MyD88 shows increased development of T1DM under GF conditions (Wen et al. 2008). MyD88 deficiency changes the composition of gut microbiota and leads to T1DM by regulating host immune response (Wen et al. 2008).

4.7 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder which is caused by obliteration of bone and cartilage which leads to development of pain and swelling in and around the joints of body. It is very frequent disease affecting 1% of total population and is quite common among females.

RA correlates with the inflammatory responses caused by $CD4^+$ Th1 and Th17 cells and any variation in these responses leads to advancement of RA (Xu et al. 2019). Study on collagen induction arthritis (CIA) mice model shows that gut microbiota plays crucial role in impacting susceptibility to arthritis. The gut microbiota of CIA-susceptible and CIA-resistant mice was altered (Liu et al. 2016). It is also reported that the GF mice having microbiota of CIA-susceptible mice show increased initiation of RA than those having microbiota of CIA-resistant mice (Liu et al. 2016).

4.8 Inflammatory Bowel Disease (IBD)

IBD is a gastrointestinal disorder in which structure of mucosa gets altered, composition of gut microbiota changes along with some systemic deformity (Mulder et al. 2014). Depending on the symptoms and intestinal localization it is mainly divided in two forms, Crohn's disease (CD) and ulcerative colitis (UC) (Mulder et al. 2014; Wijmenga 2005). IBD is a progressive disease and its frequency increased worldwide (Chow et al. 2009; Kaplan 2015; Wang et al. 2010). Recent research points out the role of gut microbiota in development of IBD, Th17, and Treg cells harmony is crucial for intestinal homeostasis. Study on segmented filamentous bacteria (SFB) in mice reveals the inflation of Th1 and Th17 cytokines (Gaboriau-Routhiau et al. 2009; Ivanov et al. 2009; Lee and Mazmanian 2014).

Several studies suggested that IBD patients with dysbiosis show alteration in their stool microbiome as well as loss of beneficial microorganisms compared to that of healthy individuals (Moustafa et al. 2018). The cause and development of IBD is linked with dysbiosis in various reports (Abu-Shanab and Quigley 2010; Casén et al. 2015; Huttenhower et al. 2014; Marchesi et al. 2007; Tamboli et al. 2004; Wright et al. 2015; Zhang et al. 2007). In IBD patients, number of commensal bacteria such as Firmicutes and Bacteroides are comparatively less in number; however, bacteria of family *Enterobacteriaceae* are higher in number (Bien et al. 2013; Hedin et al. 2014; Li et al. 2015; Mondot et al. 2011; Nguyen 2011). Another study reports the interaction between reduced gut diversity and disease onset in individuals with CD (Gevers et al. 2014). The studies performed in CD and UC individuals reveal decrease in *Clostridium* groups of bacteria and increase in Proteobacteria (Frank et al. 2007; Macpherson et al. 2000; Sartor 2008), as well as compelling reduction of commensal bacterial species belong to genera *Bacteriodes*, *Lactobacillus*, and *Eubacterium* (Nemoto et al. 2012; Sha et al. 2013).

4.9 Celiac Disease (CD)

It is a chronic disorder of the digestive system. Gut microbiota plays pivotal role in onset of this disease, any alteration in the composition of gut microbiota leads to the CD (Festi et al. 2014). It is hypothesized that gut microbiota have pathogenic role in CD development (Collado et al. 2007). Studies show that species like *Streptococcus mutans* and *Streptococcus anginosus* were present in less number in CD patients compared to that of healthy individuals (Lazar et al. 2018). Galactoside 2-alpha-L-fucosyltransferase2 is an enzyme which is encoded by *FUT2* gene; monitors the expression of ABH blood group antigens in intestinal mucus as well as other secretions. Study conducted in Fut2-deficient mice illustrates higher susceptibility to *Candida albicans* colonization compared to that of control mice, this leads to induction of CD (Lazar et al. 2018). *Bifidobacterium* spp. of bacteria are commensal of gut and provide protection against pathogens, any changes in the microbiome due to mutation in *FUT2* gene lead to development of CD (Nagao-Kitamoto et al. 2016).

4.10 Systemic Lupus Erythematosus (SLE)

SLE as the name suggests is a systemic, chronic, and inflammatory autoimmune disease of ambiguous mechanism mainly defines by inflammation at multiple site of the body (Paglia et al. 2017). Manifestation of this disease is indicated by upsurge of *Bacteroides* phyla and reduction in *Firmicutes* (Hevia et al. 2014). The composition of microbiota is believed to be crucial, as any modification in microbiota is associated with onset of SLE. There are several reports which explained the link between dysbiosis and SLE development. Recent study shows that microbiomes of SLE patients of northeastern China have higher number of Proteobacteria and lesser number of Ruminococcaceae (Wei et al. 2019).

4.11 Cancer

The major factor which is pivotal for cancer development is chronic inflammation. Inflammation accelerates the tumor development and hastens invasion and metastasis. Inflammatory cytokines cause damage in the DNA, any changes in the methylation of DNA induce inflammation-associated cancers (Nagao-Kitamoto et al. 2016). Development of cancer is not associated with change in single entity; however, it is linked with dysbiosis of entire microbiome. During dysbiosis, there is alteration in the bacterial populations with upsurge in tumor-inducing species and decrease in commensal species (Lazar et al. 2018). During inflammation, there is increased alteration of microbiota which assists bacterial translocation into the neoplastic tissue and leads to expression of inflammatory cytokines which in turn causes tumor growth (Grivennikov et al. 2012). The microbiota of the colon induces colorectal cancer by triggering immune response of Th17 cells (Wu et al. 2009).

The balance between microbiota and host defense mechanism is crucial for the development of colorectal cancer.

4.12 Conclusion and Future Perspectives

The diversity and dynamics of human microbiome are intriguing and therefore there is increased research in this direction in the past decade. Eubiosis of the microbiome is crucial for the host functions. The role of the gut microbiota in the development of the host immune system and autoimmune disorder is already evident from the research. Host genetics and environmental cues are pivotal in shaping the gut microbiota. Any modulation in gut microbiota increases the prospect of autoimmune disease.

This chapter highlights the association between the gut microbiota with immune system and disease development. The identification and characterization of crucial microorganism and their mechanism of action will allow us to understand their contribution in disease development and progression, as well as lead the way for the development of novel strategies which can prevent disease development. Apart from this, human microbiome can also be used to identify gut-associated disease as change in gut microbiota is a hallmark in various gut-linked diseases. Considering the fact that microbiome can change upon dietary changes this could be used to customize diets which can reshape microbiota and its function in order to prevent disease. This knowledge can be used in future for accurate and efficient treatment of patients. Further recognition of unique symbiotic microorganism which prevents aggregation of disease causing bacteria and boosts host immunity will pave a way in development of medicine which can reverse the defects caused by dysbiosis.

Acknowledgments I gratefully acknowledge the University Grants Commission (UGC), Government of India for awarding Junior and Senior Research Fellowship.

Conflict of Interest Author has no conflict of interest.

References

Aagaard K et al (2014) The placenta harbors a unique microbiome. Sci Transl Med 6(237):237ra65

Aathira R, Jain V (2014) Advances in management of Type 1 diabetes mellitus. World J Diabetes 5 (5):689–696

Abu-Shanab A, Quigley EMM (2010) The role of the gut microbiota in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 7(12):691–701

Adachi S, Yoshida H, Kataoka H, Nishikawa S (1997) Three distinctive steps in Peyer's patch formation of murine embryo. Int Immunol 9(4):507–514

Allin KH, Nielsen T, Pedersen O (2015) Mechanisms in endocrinology: gut microbiota in patients with type 2 diabetes mellitus. Eur J Endocrinol 172(4):R167–R177

Ardissone AN et al (2014) Meconium microbiome analysis identifies Bacteria correlated with premature birth. PLoS One 9(3):e90784

Bandeira A et al (1990) Localization of gamma/Delta T cells to the intestinal epithelium is independent of Normal microbial colonization. J Exp Med 172(1):239–244
Benoit C, Ley RE, Gewirtz AT (2014) Intestinal epithelial cell toll-like receptor 5 regulates the intestinal microbiota to prevent low-grade inflammation and metabolic syndrome in mice. Gastroenterology 147(6):1363–1377
Berg D, Clemente JC, Colombel J-F (2015) Can inflammatory bowel disease be permanently treated with short-term interventions on the microbiome? Exp Rev Gastroenterol Hepatol 9 (6):781–795
Bien J, Palagani V, Bozko P (2013) The intestinal microbiota Dysbiosis and Clostridium Difficile infection: is there a relationship with inflammatory bowel disease? Ther Adv Gastroenterol 6 (1):53–68
Bouskra D et al (2008) Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature 456(7221):507–510
Brandtzaeg P, Kiyono H, Pabst R, Russell MW (2008) Terminology: nomenclature of mucosa-associated lymphoid tissue. Mucosal Immunol 1(1):31–37
Brugman S et al (2006) Antibiotic treatment partially protects against type 1 diabetes in the bio-breeding diabetes-prone rat. Is the gut Flora involved in the development of type 1 diabetes? Diabetologia 49(9):2105–2108
Carasi P et al (2015) Impact of kefir derived Lactobacillus Kefiri on the mucosal immune response and gut microbiota. J Immunol Res 2015:361604
Carvalho FA et al (2012) Transient inability to manage Proteobacteria promotes chronic gut inflammation in TLR5-deficient mice. Cell Host Microbe 12(2):139–152
Casén C et al (2015) Deviations in human gut microbiota: a novel diagnostic test for determining Dysbiosis in patients with IBS or IBD. Aliment Pharmacol Ther 42(1):71–83
Chassaing B et al (2014) AIEC Pathobiont instigates chronic colitis in susceptible hosts by altering microbiota composition. Gut 63(7):1069–1080
Chow DKL et al (2009) Long-term follow-up of ulcerative colitis in the Chinese population. Am J Gastroenterol 104(3):647–654
Clarke TB et al (2010) Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med 16(2):228–231
Clemente JC, Ursell LK, Parfrey LW, Knight R (2012) The impact of the gut microbiota on human health: an integrative view. Cell 148(6):1258–1270
Collado MC, Calabuig M, Sanz Y (2007) Differences between the fecal microbiota of coeliac infants and healthy controls. Curr Issues Intest Microbiol 8(1):9–14
Corthésy B (2013) Multi-faceted functions of secretory IgA at mucosal surfaces. Front Immunol 4:185
Couturier-Maillard A et al (2013) NOD2-mediated Dysbiosis predisposes mice to transmissible colitis and colorectal Cancer. J Clin Invest 123(2):700–711
Crabbé PA, Bazin H, Eyssen H, Heremans JF (1968) The Normal microbial Flora as a major stimulus for proliferation of plasma cells synthesizing IgA in the gut. The germ-free intestinal tract. Int Arch Allergy Appl Immunol 34(4):362–375
Cullender TC et al (2013) Innate and adaptive immunity interact to quench microbiome flagellar motility in the gut. Cell Host Microbe 14(5):571–581
De Martino SJ et al (2004) Peripartum Bacteremias due to Leptotrichia Amnionii and Sneathia Sanguinegens, rare causes of fever during and after delivery. J Clin Microbiol 42 (12):5940–5943
Devaraj S, Dasu MR, Park SH, Jialal I (2009) Increased levels of ligands of toll-like receptors 2 and 4 in type 1 diabetes. Diabetologia 52(8):1665–1668
Dominguez-Bello MG et al (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 107 (26):11971–11975

Dwivedi M, Ansarullah, Radichev I, Kemp EH (2017) Alteration of immune-mechanisms by human microbiota and development and prevention of human diseases. J Immunol Res 2017:6985256
Elinav E et al (2011) NLRP6 Inflammasome regulates colonic microbial ecology and risk for colitis. Cell 145(5):745–757
Endesfelder D et al (2014) Compromised gut microbiota networks in children with anti-islet cell autoimmunity. Diabetes 63(6):2006–2014
Fagarasan S et al (2002) Critical roles of activation-induced cytidine deaminase in the homeostasis of gut flora. Science 298(5597):1424–1427
Festi D et al (2014) Gut microbiota and metabolic syndrome. World J Gastroenterol 20 (43):16079–16094
Frank DN et al (2007) Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A 104 (34):13780–13785
Fulde M et al (2018) Neonatal selection by toll-like receptor 5 influences long-term gut microbiota composition. Nature 560(7719):489–493
Gaboriau-Routhiau V et al (2009) The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T-cell responses. Immunity 31(4):677–689
Gérard P (2013) Metabolism of cholesterol and bile acids by the gut microbiota. Pathogens 3 (1):14–24
Gevers D et al (2014) The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe 15(3):382–392
Gordon Jeffrey I, Dewey KG, Mills DA, Medzhitov RM (2012) The human gut microbiota and undernutrition. Sci Transl Med 4(137):137ps12
Grivennikov SI et al (2012) Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 491(7423):254–258
Gülden E et al (2013) Toll-like receptor 4 deficiency accelerates the development of insulin-deficient diabetes in non-obese diabetic mice. PLoS One 8(9):e75385
Han H et al (2018) Gut microbiota and type 1 diabetes. Int J Mol Sci 19(4):251–259
Hedin CR et al (2014) Altered intestinal microbiota and blood T-cell phenotype are shared by patients with Crohn's disease and their unaffected siblings. Gut 63(10):1578–1586
Helgeland L et al (2004) Microbial colonization induces Oligoclonal expansions of intraepithelial CD8 T cells in the gut. Eur J Immunol 34(12):3389–3400
Hevia A et al (2014) Intestinal dysbiosis associated with systemic lupus erythematosus. mBio 5(5): e01548–e01514
Hirota K et al (2013) Plasticity of Th17 cells in Peyer's patches is responsible for the induction of T cell-dependent IgA responses. Nat Immunol 14(4):372–379
Hooper LV, Stappenbeck TS, Hong CV, Gordon JI (2003) Angiogenins: a new class of Microbicidal proteins involved in innate immunity. Nat Immunol 4(3):269–273
Human Microbiome Project Consortium (2012) Structure, function and diversity of the healthy human microbiome. Nature 486(7402):207–214
Huttenhower C, Kostic AD, Xavier RJ (2014) Inflammatory bowel disease as a model for translating the microbiome. Immunity 40(6):843–854
Imaoka A et al (1996) Proliferative recruitment of intestinal intraepithelial lymphocytes after microbial colonization of germ-free mice. Eur J Immunol 26(4):945–948
Ivanov II et al (2009) Induction of intestinal Th17 cells by segmented filamentous Bacteria. Cell 139 (3):485–498
Jiao Y, Wu L, Huntington ND, Zhang X (2020) Crosstalk between gut microbiota and innate immunity and its implication in autoimmune diseases. Front Immunol 11:282
Kaplan GG (2015) The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 12(12):720–727
Kato LM, Kawamoto S, Maruya M, Fagarasan S (2014) The role of the adaptive immune system in regulation of gut microbiota. Immunol Rev 260(1):67–75

Kawaguchi-Miyashita M et al (1996) Development and Cytolytic function of intestinal intraepithelial T lymphocytes in antigen-minimized mice. Immunology 89(2):268–273
Lagier J-C et al (2012) Microbial Culturomics: paradigm shift in the human gut microbiome study. Clin Microbiol Infect 18(12):1185–1193
Larsson E et al (2012) Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88. Gut 61(8):1124–1131
Lazar V et al (2018) Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and Cancer. Front Immunol 9:1830
Lee YK, Mazmanian SK (2014) Microbial learning lessons: SFB educate the immune system. Immunity 40(4):457–459
Levy M, Thaiss CA, Elinav E (2015) Metagenomic cross-talk: the regulatory interplay between Immunogenomics and the microbiome. Genome Med 7:120
Li J, Butcher J, Mack D, Stintzi A (2015) Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease. Inflamm Bowel Dis 21(1):139–153
Liu X et al (2016) Role of the gut microbiome in modulating arthritis progression in mice. Sci Rep 6:30594
Mabbott NA et al (2013) Microfold (M) cells: important Immunosurveillance posts in the intestinal epithelium. Mucosal Immunol 6(4):666–677
Macpherson AJ et al (2000) A primitive T cell-independent mechanism of intestinal mucosal IgA responses to commensal bacteria. Science 288(5474):2222–2226
Marchesi JR et al (2007) Rapid and noninvasive Metabonomic characterization of inflammatory bowel disease. J Proteome Res 6(2):546–551
McDermott AJ, Huffnagle GB (2014) The microbiome and regulation of mucosal immunity. Immunology 142(1):24–31
Mebius RE, Rennert P, Weissman IL (1997) Developing lymph nodes collect CD4+CD3- LTbeta+ cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. Immunity 7 (4):493–504
Medzhitov R et al (1998) MyD88 is an adaptor protein in the HToll/IL-1 receptor family signaling pathways. Mol Cell 2(2):253–258
Mirpuri J et al (2014) Proteobacteria-specific IgA regulates maturation of the intestinal microbiota. Gut Microbes 5(1):28–39
Mondot S et al (2011) Highlighting new phylogenetic specificities of Crohn's disease microbiota. Inflamm Bowel Dis 17(1):185–192
Moustafa A et al (2018) Genetic risk, Dysbiosis, and treatment stratification using host genome and gut microbiome in inflammatory bowel disease. Clin Transl Gastroenterol 9(1):e132
Mowat AMI (2003) Anatomical basis of tolerance and immunity to intestinal antigens. Nat Rev Immunol 3(4):331–341
Mulder DJ, Noble AJ, Justinich CJ, Duffin JM (2014) A tale of two diseases: the history of inflammatory bowel disease. J Crohns Colitis 8(5):341–348
Nagao-Kitamoto H, Kitamoto S, Kuffa P, Kamada N (2016) Pathogenic role of the gut microbiota in gastrointestinal diseases. Intest Res 14(2):127–138
Neish AS (2009) Microbes in gastrointestinal health and disease. Gastroenterology 136(1):65–80
Nemoto H et al (2012) Reduced diversity and imbalance of fecal microbiota in patients with ulcerative colitis. Dig Dis Sci 57(11):2955–2964
Nguyen GC (2011) Editorial: bugs and drugs: insights into the pathogenesis of inflammatory bowel disease. Am J Gastroenterol 106(12):2143–2145
Nigro G et al (2014) The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell protection and links microbes to gut epithelial regeneration. Cell Host Microbe 15(6):792–798
Opazo MC et al (2018) Intestinal microbiota influences non-intestinal-related autoimmune diseases. Front Microbiol 9:432
Ostman S et al (2006) Impaired regulatory T-cell function in germ-free mice. Eur J Immunol 36 (9):2336–2346

Pabst O (2012) New concepts in the generation and functions of IgA. Nat Rev Immunol 12 (12):821–832
Paglia L, Concetta GM et al (2017) One year in review 2017: systemic lupus erythematosus. Clin Exp Rheumatol 35(4):551–561
Palm NW, de Zoete MR, Flavell RA (2015) Immune-microbiota interactions in health and disease. Clin Immunol 159(2):122–127
Pearson JA, Susan Wong F, Wen L (2016) The importance of the non obese diabetic (NOD) mouse model in autoimmune diabetes. J Autoimmun 66:76–88
Peterson DA, McNulty NP, Guruge JL, Gordon JI (2007) IgA response to symbiotic Bacteria as a mediator of gut homeostasis. Cell Host Microbe 2(5):328–339
Petnicki-Ocwieja T et al (2009) Nod2 is required for the regulation of commensal microbiota in the intestine. Proc Natl Acad Sci U S A 106(37):15813–15818
Pociot F, Lernmark Å (2016) Genetic risk factors for type 1 diabetes. Lancet 387 (10035):2331–2339
Pussinen PJ et al (2011) Endotoxemia is associated with an increased risk of incident diabetes. Diabetes Care 34(2):392–397
Qin J et al (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464(7285):59–65
Rakoff-Nahoum S et al (2004) Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 118(2):229–241
Ramanan D et al (2014) Bacterial sensor Nod2 prevents inflammation of the small intestine by restricting the expansion of the commensal Bacteroides Vulgatus. Immunity 41(2):311–324
Ranucci G et al (2017) Early-life intestine microbiota and lung health in children. J Immunol Res 2017:8450496
Rewers M, Ludvigsson J (2016) Environmental risk factors for type 1 diabetes. Lancet 387 (10035):2340–2348
Round JL et al (2011) The toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 332(6032):974–977
Salzman NH, Bevins CL (2013) Dysbiosis--a consequence of Paneth cell dysfunction. Semin Immunol 25(5):334–341
Salzman NH et al (2010) Enteric Defensins are essential regulators of intestinal microbial ecology. Nat Immunol 11(1):76–83
Sartor RB (2008) Microbial influences in inflammatory bowel diseases. Gastroenterology 134 (2):577–594
Sekirov I, Russell SL, Caetano L, Antunes M, Brett Finlay B (2010) Gut microbiota in health and disease. Physiol Rev 90(3):859–904
Seksik P, Landman C (2015) Understanding microbiome data: a primer for clinicians. Digest Dis 33 (Suppl 1):11–16
Sha S et al (2013) The biodiversity and composition of the dominant fecal microbiota in patients with inflammatory bowel disease. Diagn Microbiol Infect Dis 75(3):245–251
Sonnenburg JL, Bäckhed F (2016) Diet-microbiota interactions as moderators of human metabolism. Nature 535(7610):56–64
Stewart CJ et al (2018) Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 562(7728):583–588
Suzuki K et al (2004) Aberrant expansion of segmented filamentous Bacteria in IgA-deficient gut. Proc Natl Acad Sci U S A 101(7):1981–1986
Tamboli CP, Neut C, Desreumaux P, Colombel JF (2004) Dysbiosis in inflammatory bowel disease. Gut 53(1):1–4
Todd JA et al (2007) Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 39(7):857–864
Tsuji M et al (2009) Preferential generation of follicular B helper T cells from Foxp3+ T cells in gut Peyer's patches. Science 323(5920):1488–1492

Vaishnava S et al (2011) The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 334(6053):255–258
Velloso LA, Folli F, Saad MJ (2015) TLR4 at the crossroads of nutrients, gut microbiota, and metabolic inflammation. Endocr Rev 36(3):245–271
Vijay-Kumar M et al (2010) Metabolic syndrome and altered gut microbiota in mice lacking toll-like receptor 5. Science 328(5975):228–231
Virili C et al (2018) Gut microbiota and Hashimoto's thyroiditis. Rev Endocr Metab Disord 19 (4):293–300
Wang YF, Ouyang Q, Ren Wei H (2010) Progression of inflammatory bowel disease in China. J Dig Dis 11(2):76–82
Wei F et al (2019) Changes of intestinal Flora in patients with systemic lupus erythematosus in Northeast China. PLoS One 14(3):e0213063
Wen L et al (2008) Innate immunity and intestinal microbiota in the development of type 1 diabetes. Nature 455(7216):1109–1113
Wesche H et al (1997) MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. Immunity 7(6):837–847
Wijmenga C (2005) Expressing the differences between crohn disease and ulcerative colitis. PLoS Med 2(8):e230
Wright EK et al (2015) Recent advances in characterizing the gastrointestinal microbiome in Crohn's disease: a systematic review. Inflamm Bowel Dis 21(6):1219–1228
Wu H-J, Eric W (2012) The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 3(1):4–14
Wu S et al (2009) A human colonic commensal promotes colon tumorigenesis via activation of T-helper type 17 T-cell responses. Nat Med 15(9):1016–1022
Xu H et al (2019) The dynamic interplay between the gut microbiota and autoimmune diseases. J Immunol Res 2019:7546047
Zhang H et al (2015) Host adaptive immunity alters gut microbiota. ISME J 9(3):770–781
Zhang M et al (2007) Structural shifts of mucosa-associated lactobacilli and Clostridium Leptum subgroup in patients with ulcerative colitis. J Clin Microbiol 45(2):496–500