Role of Gut Microbiome Composition in Shaping Host Immune System Development and Health

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Abstract

The gut microbiome is a community of commensal microbes in the gastrointestinal tract that are ecologically, physiologically, and symbiotically associated with the host from the early days of life. Gut microbiota is analogous to endocrine glands. Microbial colonies in the gut produce certain microbial metabolites from nutrient metabolism. These gut-derived metabolites regulate the host's health and disease by influencing immunity and physiology. Gut microbiota protects the intestinal environment from invading non-native pathogens by immune modulation and direct competition with pathogens for nutrient access. The gut microbiome is essential in regulating the immune system through interaction with its microbial surface antigens and metabolites. Gut microbiota is coevolved with host development and varies among individuals. The proportion of gut microbiota is constant during health. This constancy is affected by factors such as diet, medications, environment, and mental status regulating the host's health. The dysbiotic microbiome is a risk signature of immune dysfunction and disorders in host physiology. The gut microbiome modulates the immune system locally and systematically; thus, its composition balances an individual's health

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and disease conditions. This chapter reviewed the link between microbiome composition and its outcome on host physiology, immune system development, metabolic syndromes, and cancer outcomes.

Keywords

Gut microbiome · Immune system · Metabolic disorders · Microbial metabolites · Innate immunity · Adaptive immunity

3.1 Introduction

The human body harbors trillions of microbial communities in the gastrointestinal (GI) tract called gut microbiome. Joshua Lederberg explained gut microbiota as "The community of microorganisms presents in the gastrointestinal tract of the host" (Bäckhed et al. 2005; Neish 2009). The gut microbiota is considered a completely evolved and established organ in the human body analogous to hormone-secreting endocrine glands. Gut microbiota regulates multifarious physiological and metabolic pathways via its derived metabolites as substrates and maintains immunohomeostatic comprehensive cellular functions through cell signaling and biochemical cascades (Cox and Blaser 2013). Gut microbiota is recorded as an extension to the host genome by 150 times more than the human genome. It is estimated to contain 3.3 million microbial genes that code for certain essential enzymes not included in the set of native human proteomes. The enzymes coded by genes in the microbiome catalyze several biochemical processes in nutrient absorption and metabolism (Rodríguez et al. 2015; Bäckhed et al. 2005). Recent studies from researchers relevant to metagenomics, molecular biology, and microbiology delineated the human body as a mutualistic superorganism of eukaryotic and prokaryotic microbial communities (Szablewski 2018). Hosts provide nutrition and shelter to the microbes in the gut; in turn, gut microbiota establishes its mutualistic and symbiotic nature by providing the host with better immunity and physiometabolic health. Trillions of microbes from hundreds of species constitute healthy microflora in the host gut. Of all the microbial communities, members of Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria classes are the major contributors to gut microbiome composition (Senghor et al. 2018).

Balance among the proportion of gut microbiota and these members directs the fate of host health. Microbial colonization in the GI tract began before birth. Reports from the placental microbiome characterization showed similarities with the oral microbiome of healthy adults (Aagaard et al. 2014). In neonates, lactating has a defensive effect, deliberated by an intricate combination of lysozymes, sIgA, α-lactalbumin, free oligosaccharides, complex lipids, and other glycoconjugates (Gordon et al. 2012). Oligosaccharides such as fructans are prebiotic factors that help the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*. Understanding the gut microbiome unravels microbial-mediated immune and metabolic regulation mechanisms in the host body. Studying the entire microbial communities in the host GI tract was a challenge to researchers and scientists during the

initial days when gut microbiota composition was analyzed based on culture methods. These methods are inadequate to examine the total profile of the gut microbiome; as a result, only 10–50% of the intestinal microbes were probably cultured. In recent years, understanding of gut microbiota increased with advanced sequencing technologies adapting next-generation sequencing approaches, metagenomics, and advancements in bioinformatics tools to handle and analyze the downstream data from sequencers ensured in estimating several classes of microbes and their phylogenetic relationships. The qualitative analysis of gut microbiota is mostly delineated using techniques like DNA fingerprinting, terminal RFLP, 16 s ribosomal RNA amplicon sequencing, microarray technique, and whole genome sequencing, which provided enormous data about the total microbial population. High-throughput sequencing technologies like Roche/454, GS20, Illumina's Genome Analyzer IIx, Affymetrix microarray technique, and Qiagen's Gene Read are tremendously eminent.

Moreover, advanced bioinformatics tools have assisted in understanding and illustrating the downstream analysis of sequence data. The gut microbiota is highly reactive and adaptive to dietary alterations, medication choice, genetic factors, and the host's lifestyle. After weaning to solid foods, exorbitant modifications appear in the composition of their gut microbiota. Changes in the microbiota (Dysbiosis) could lead to numerous health disorders such as obesity, nonalcoholic fatty liver disease (NAFLD), diabetes, inflammatory bowel disease, ulcerative colitis, colorectal cancer, coronary heart disease, autoimmune diseases, and neurological disorders. The gut microbiome has become a major tool and a potential clinically important marker for diagnosing and treating many diseases in the body. Modulating or redirecting the gut microbiota to its native state (eubiosis) is an ideal and promising strategy for simulating host immunity. Reconstituting the gut microbial communities benefits the host with better health and immunity. Engineering gut environment with probiotic supplements, prebiotics, and functional foods effectively shapes host immunity. The importance of gut microbiota in immune system development and modulation, along with its fate in disease and health conditions, are discussed clearly in this chapter addressing the recent findings and outbreaks in gut microbiome research in correlation with host immunity and health.

3.2 Intestinal Microbiota and Host Immunity

The gut microbiota considerably regulates innate and adaptive immune system functions and development. The host's immune system has two protective mechanisms: innate immunity, specified as an immediate and nonspecific response against the pathogen. And another one is adaptive immunity which ensures both memory and specificity. In the innate immune response, secretory IgA (sIgA) plays a significant role and is a protective mechanism against infectious agents. The production of sIgA over various mucosal surfaces is through the entry of antigens and their subsequent capture through Peyer's patches, M cells, stimulation of T cells, dendritic cells (DCs), and changes in B cells to mesenteric lymph nodes (MLNs)

recombination and lymphoid tissue connected to the gut. The group of cytokines such as IL-4, IL-5, IL-10 and including TGF-β increases the production of IgA. The sIgA binds to commensal bacteria and contributes to the gut barrier function and intestinal mucosal homeostasis (Chairatana and Nolan 2017).

The innate immune cells like DCs, natural killer (NK) cells, and macrophages express pattern recognition receptors (PRRs) that recognize specific molecular patterns on the bacterial surface, which are key mediators for communication between gut microbiota and the host (Pahari et al. 2018, 2019; Negi et al. 2019). These PRRs recognize pathogen- or microbe-associated molecular patterns (PAMPs or MAMPs) on the bacterial surface. PRRs majorly contain families of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs) (Kumar et al. 2011). Identifying microbiota through PRRs promotes memory response on primary exposure (Mills 2011; Kleinnijenhuis et al. 2012). The TLRs exist on DCs, macrophages, intestinal epithelial cells (ECs), neutrophils, and other innate immune cells. The microbial products and metabolites alter the host immune system by stimulating different types of cells like intestinal epithelial cells (IECs), mononuclear phagocytes, innate lymphoid cells (ILCs), B cells, and T cells (Kabat et al. 2014).

The GI tract protects the host from habitat and interceding nutrient consumption. The IECs on the intestinal surface form a physical barrier that detaches the lumen from the lamina propria of commensal and intestinal microbes. Although IECs are not typical innate immune cells, these are essential in mucosal immunity. Despite this, IECs are armed with innate immune system receptors that could provide gut equilibrium by recognizing bacteria (Pott and Hornef 2012). ILCs are infrequent innate lymphocytes when correlated with adaptive lymphocytes, yet these are copious on the surface barrier of mucosal-connected tissues (Sonnenberg and Artis 2012). Several research studies demonstrated that specific microbiota metabolites could control ILCs (Lee et al. 2012) expressing IL-22 cytokine. The inadequacy of IL-22 is connected with various inflammations and metabolic diseases. IL-22 also elevates the antimicrobial peptides production (RegIIIγ and RegIIIβ) to reduce the SFB colonization, stimulate the surface proteins fucosylation to intensify the beneficial bacteria colonization, and increase the goblet cells proliferation for secretion of mucin (Goto et al. 2014). Based on T domain structures, the T cells can be further segregated into γδ T and αβ T cells. αβ TCR cells expressed by T cells are initially liable for antigen-specific cellular immunity, and γδ T cells are not MHC—restricted also engaged in initial immune responses (Pennington et al. 2005). Despite this, in the small intestine of murine, γδ TCR chains are expressed by a higher proportion of intraepithelial lymphocytes (IELs) (van Wijk and Cheroutre 2009). These γδ IELs specifically regulate IECs' continuous turnover and increase the growth of epithelial cells by keratinocyte secretion, an in vitro growth factor (Boismenu and Havran 1994). The γδ IELs also maintain the functions of the epithelial barrier by inhibiting pathogen reincarnation (Dalton et al. 2006). The association of innate and adaptive immune systems is involved in eliminating invasive pathogens and regulating symbiotic bacteria at mucosal sites. The antigen-presenting cells like naïve CD4+ αβ T cells ($CD4^+$ T cells) and DCs are further characterized into Th1, Th2,

and Th17 or adaptive T-regulatory cells (Tregs). All these cells exist in intestinal lamina propria. Th17 is the group of $CD4^{+}$T cells that secretes numerous cytokines (IL-22, IL-17F, and IL-17A) (Rossi and Bot 2013), including notable effects upon inflammation and immune homeostasis. These cells also retain various cytokine characteristic analyses and functions. Th1 and Th2 cells have a steady secretory analysis after differentiation. Tregs are essential mediators of immune tolerance, reducing an improper, immense inflammatory reaction, and their malfunctions lead to autoimmune disorders. Of interest, in the germfree mice administered with a lustrated dose of polysaccharide or by intestinal colonization with commensal bacteria, a non-toxigenic form of *B. fragilis* which expresses polysaccharide A (PSA), prevents the growth of experimental colitis by PSA-induced $Foxp3^{+}$-regulatory cells expressed by IL-10, through TLR2-dependent action (Round and Mazmanian 2010). In commensal microbiota, a few microbes have a higher effect on the responses of mucosal T cells. For instance, in Th17 cells of the small intestine, segmented filamentous bacteria (SFB) are effective stimulators; in germfree mice, it was observed by the lack of Th17 cells and their revival when SFB colonized in germfree mice (Ivanov et al. 2009a). In the gut, the abundant presence of retinoic acid (RA) activates lymphocyte gut-homing compounds and restricts the growth of Th17 cells (Mucida et al. 2007); still, the mechanism of regulation of Th17 gut tropism is unknown (Maynard and Weaver 2009). Therefore, intestinal lamina propria is an elemental site for the evolution of Th17, probably by the colonization of SFB and the expression of innate IL-23 in the intestinal microhabitat.

3.3 Gut Microbiota Metabolism

Intestinal microbiota regulates various host physiological mechanisms such as nutrient uptake, energy expenditure, and immune responses through metabolism. Gut microbiome-derived metabolites act as substrates for various cell signaling processes and host metabolic pathways and can alter the immune responses post-maturation and differentiation. Gut microbiota-derived metabolites are crucial in health and disease conditions in the host. According to recent investigations and reports, over 50% of the metabolome in stool and urine are derivatives of modulated gut microbiota. The microbiota metabolites are bioactive and intensely affect physiology and host immunity (Donia and Fischbach 2015). The following sections further discuss the role of gut microbial metabolites and their metabolic actions.

3.3.1 Retinoic Acid (RA) Metabolism

Retinoic acid (RA), a lipid metabolite of vitamin A, can regulate the equity among pro-inflammatory and anti-inflammatory immune reactions. RA inadequacy can run down the orchestration of gut microbiota and immune system activities. In constant conditions, RA is pivotal in maintaining intestinal immune homeostasis since it

facilitates the regulatory T-cell progression by TGF-β and the formation of IgA through B cells (Mucida et al. 2007). It is perplexing that RA is also entangled in drawing out pro-inflammatory CD4+ T-cell reactions to diseases during inflammation—other vitamins like vitamin D extremely influence T-cell activation. Multifarious research analyses have associated vitamin D inadequacy with inflammatory bowel disease. The hook-up between the intestinal microbiota and vitamins is conspicuous in vitamins of B and K groups (Martens et al. 2002). The inadequacy of vitamin B12 leads to a reduced count of lymphocytes and induces NK cell functioning.

3.3.2 Tryptophan Metabolism

Inadequacy of innate immunity pathways results in malfunction of gut microbe. For instance, complex proteins and carbohydrates which are unable to degrade by the host can be digested by microbial colonies. Gut microbiota influences tissue-level immune development through the catabolism of tryptophan. The *Lactobacillus* utilizes tryptophan as a vitality source to form ligands of the aryl hydrocarbon receptors (AhR) like the metabolite indole-3-aldehyde (Nicholson et al. 2012).

3.3.3 Short Chain Fatty Acids (SCFAs) Metabolism

The microbiome provides mammalian enzymes to degrade dietary nondigestible carbohydrates (NDCs) adherent starch by fermentation into short-chain fatty acids (SCFAs) in the GI tract (Holscher 2017). SCFAs are known as carboxylic acids, including 1–6 aliphatic carbon tails such as acetate, propionate, and butyrate produced in a molar ratio of approximately 60:20:20, respectively (den Besten et al. 2013), and other end products consist of ethanol, succinate, formate, valerate, isobutyrate, and 2-methyl butyrate. SCFAs potentiate colonocytes, and inhabitant bacteria, decrease GI luminal pH to reduce pathogen growth, regulate anti-inflammatory and immunostimulatory properties, and endorse bile acid secretion, which aids in the digestion of dietary fats and increases mineral absorption (Schuijt et al. 2016). The SCFAs are proposed to engage certain G-protein-coupled receptors (GPR41, GPR43). GPR109a are stimulated through ionized SCFA, increasing the excretion of peptide YY, glucagon-like peptide (GLP-1), enhanced glucose usage, and reduced fatty acid metabolism (Koh et al. 2016). SCFAs are recorded to defend from diet-induced obesity, regulate gene expression, and induce anti-inflammatory reaction and apoptosis. In addition, SCFAs stimulate lipid metabolism by increasing lipogenesis and preventing fatty acid oxidation, as formerly recorded. SCFAs are crucial in colonic health, notably in protecting and differentiating epithelial cells. Some of the known well-characterized transporters and receptors of SCFAs are given in Table 3.1. SCFAs also regulate the expression of inflammatory cytokines like IL-6, IL-7, IL-8, IL-12, IL-1β, and TNF-α by colonic epithelial cells (Asarat et al. 2015), regulating blood pressure, leading to gut-barrier dysfunction. Butyrate is an energy

Table 3.1 Transporters and receptors of SCFAs

Transporters of SCFAs					
Transporter molecule	Function	SCFAs	Model organism	Cell/tissue	References
MCT1	A H+-coupled transporter for SCFAs and related organic acids	Butyrate, pyruvate, lactate	Human	Distal colon> proximal colon>ileum>jejunum	Gill (2005)
			Mice, rat	Cecum>colon>stomach and small intestine	Kirat et al. (2009)
			Human	Monocytes, lymphocytes, and granulocytes	Murray et al. (2005)
SMCT1	A Na(+)-coupled transport of monocarboxylates and ketone bodies into various cell types	Butyrate > propionate > lactate >>acetate	Human, mice	Distal colon>proximal colon and ileum	Borthakur et al. (2010)

Receptors of SCFAs					
Receptor	Function	SCFAs	Model organism	Cell/tissue	Reference
GPR109A	A receptor for C4 and niacin. cAMP regulation, suppression of adipocyte lipolysis, HDL metabolism, DC trafficking, antitumor activity and HDL metabolism	D-beta-hydroxybutyrate, nicotinic acid and butyrate	Human, mice	Adipose tissue	Tunaru et al. (2003)
			Human, mice	Colon	Thangaraju et al. (2009)
GPR43	A receptor for SCFAs. Secretion of PYY and GLP-1, adipocyte development, adipogenesis, suppression of lipolysis, epithelial innate immunity, antitumor activity, anti-inflammatory effect, and T-reg differentiation	Acetate=propionate=butyrate>pentanoate >hexanoate>formate	Human, mice	Colonic myeloid cells and Treg	Smith et al. (2013)
			Human	Intestinal epithelium	Agus et al. (2016)
GPR41	A receptor for SCFAs. Regulation of gut hormone, leptin production, and sympathetic activation, epithelial innate immunity	Propionate=pentanoate=butyrate> acetate>formate	Human	Monocytes, monocyte-derived dendritic cells, and Nastasi neutrophils	Nastasi et al. (2015)

substrate that intensely affects the healthy colonic epithelial barrier and immunomodulatory effects. The gut microbiota synthesizes vitamins (like B vitamins, k, biotin, folates, riboflavin, and cobalamin) and amino acids and carries out bile transformation. The antimicrobial compounds produced from microbiota contend for nutrients and gut lining attachment, thereby inhibiting the growth of pathogens. As a result, it promotes to the reduction of the lipopolysaccharides and peptidoglycans synthesis that is pernicious to the host (Tlaskova-Hogenova et al. 2004).

3.3.4 Bile Acids Metabolism

Bile acids are steroid metabolites present in bile. They are produced in the liver from cholesterol. Bile acids ensure solubility and uptake of vitamins and fats. Bile acids directly synthesized from cholesterol in the liver are primary bile acids. Primary bile acids conjugate with glycine or taurine to form secondary bile acids. Gut resident microbes deconjugate secondary BAs to primary BAs and glycine or taurine again. BAs are signaling molecules to farnesoid X receptor (FXR) and GPCR TGR5 in controlling the uptake of fats and vitamins (Tolhurst et al. 2012; Velagapudi et al. 2010).

3.3.5 Choline Metabolism

Choline is a cell membrane component and also a cationic essential nutrient. Choline is found in meat and eggs. It is essential in lipid metabolism. Enzymatic degradation of choline in the liver yields TMA (trimethylamine). TMA further metabolizes into trimethylamine N-oxide (TMAO) (Spencer et al. 2011). TMA and TMA are toxic metabolites. Production of these metabolites is controlled and regulated by microbes in the gut microbiome. Disturbance in the gut ecosystem is associated with a rise in the levels of these metabolites, which further leads to immune dysfunction and cardiometabolic syndrome (Prentiss et al. 1961; Dumas et al. 2006). Hence, the gut microbiota is key in regulating host health and metabolism.

3.4 Gut Microbiota Dysbiosis and Disease

3.4.1 IBD

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD). Ulcerative colitis (UC) is an incurable condition characterized by GI tract inflammation evoked by the consolidation of genetic, environmental, and microbial components typified by abdominal ache, diarrhea, and bloody feces (Wilson et al. 2016; Cosnes et al. 2011). The IBD is an exorbitant host immune system and gut flora stimulation in inherently affected patients (Wong and Ng 2013). The IL-23/Th17 deregulation is connected with numerous genetic sensitivity of single-nucleotide polymorphisms

(SNPs) in individuals affected with CD and UC due to deterioration of innate and adaptive immunity reactions (Yen et al. 2006). Remarkably, dysbiosis is linked with the exaggerated reproduction of the responsive oxygen category that consecutively results in alterations of intestinal microbiota composition, mucosal penetrability, and enhanced immune provocation. By way of illustration of how particular microbes produce intestinal inflammation and stimulate the pathogenesis of IBD exists in Bloom et al. (2011). In their examination, commensal Bacteroidetes strains have been secluded in IL-10r2 and Tgfbr2-insufficient mice (Bloom et al. 2011). There is a confirmation that the growth of IBD is a symbiotic impact of genetic and acquired components that results in the modulations in activities and arrangement of intestinal microbiota (Albenberg et al. 2012). Despite this, the metagenomic analysis explained that microbial ecosystem and intestinal flora were reduced in IBD-affected individuals compared with healthy adults (Hansen et al. 2010). Frequently, 25% lesser genes were discovered in the stool samples of IBD individuals than in healthy controls (Qin et al. 2010). In addition, humans with UC and CD have decreased the fewer microbes like Firmicutes (Sheehan et al. 2015; Frank et al. 2007; Walker et al. 2011) having anti-inflammatory and pro-inflammatory properties and enhanced the phyla of Bacteroidetes, Proteobacteria in mucosa-associated flora (Sokol et al. 2006). The CD-affected cases showed a lower abundance of *Faecalibacterium prausnitzii*, *Clostridium lavalense*, *Roseburia inulinivorans*, *Ruminococcus torques*, and *Blautia faecis* when correlated with healthy adults (Fujimoto et al. 2013; Takahashi et al. 2016).

Further, Sokol and co-workers demonstrated that mononuclear cells of human peripheral blood activated with *F. praunizii* to produce IL-10 and inhibit the formation of IL-12 and IFN-γ (Sokol et al. 2008). The other CD-associated *E. coli* AIEC (adherent invasive *E. coli*), which also contains pro-inflammatory features, a mucosa-associated *E. coli* with dynamic adhesive-invasive abilities, was initially isolated from CD-affected adults. Increased growth of AIEC has been observed in individuals of colonic CD, about 38% with effective ileal CD compared to healthy controls (Baumgart et al. 2007; Darfeuille-Michaud et al. 2004). As a result, the growth of pathogenic microorganisms that attach to gut epithelial cells influences intestinal penetrability, modulates the gut microbial configuration, and promotes inflammatory reactions by standardizing pro-inflammatory gene expression, eventually developing in colitis. In IBD patients, there is a reduction in the formation of SCFAs due to a decrease in the number of *F. praunizii*. *Clostridium* clusters IV, XIVa, and XVIII are butyrate-producing organisms in the gut, affecting the growth and differentiation of Tregs cells and an expansion of epithelial cells (Atarashi et al. 2013). Treg cells are CD4+ T cells that help to maintain gut homeostasis.

Furthermore, in IBD cases, there is a higher abundance of *Desulfovibrio*, which is sulfate-producing bacteria (Loubinoux et al. 2002; Zinkevich and Beech 2000). As a result, the formation of hydrogen sulfide harms the gut epithelial cells and stimulates mucosal inflammation (Loubinoux et al. 2002; Rowan et al. 2010). Accordingly, the above data indicate that gut microbial configuration changes are linked with IBD pathogenesis. The outcome of dysbiosis on IBD and the pathological changes are provided in Table 3.2.

Table 3.2 Dysbiosis in IBD and its pathological results

Dysbiosis in IBD	Outcomes of dysbiosis
↓ Firmicutes ↓ *F. praunizii* and *F. clostridium* cluster IV XIVa, XVIII ↑ *Desulfovibrio* bacteria ↑ Adherent/invasive *E. coli*	↓ Epithelial cells expansion and differentiation Change in Tregs cells differentiation ↑ Damage of epithelial cells Modulation in mucosal penetrability ↑ Bacterial invasion

↑ indicates increase, ↓ indicates decrease in level

3.4.2 Colorectal Cancer (CRC)

The World Cancer Research Foundation (WCRF), as well as the American Institute for Cancer Research (AICR), recognized that diet is one of the essential external components in CRC etiology (Dumas et al. 2016). The microbiota has been a prominent aspect of a few cancers such as breast, liver, biliary system, and CRC. Accommodating around 3×10^{13} microbes, the colorectum interplays with a huge population of microorganisms, and with that, the intestinal epithelium found a stable cross talk (Qin et al. 2010). The 16 s ribosomal RNA sequencing analyses were carried out to illustrate the CRC microbiota in stool and mucosal samples (Yu et al. 2017). Direct observation was that the microbiota of CRC individuals had undergone severe dysbiosis when correlated with the composition of healthy adults displaying numerous ecological microhabitats in individuals with CRC. In addition, certain microbes such as *Bacteroides fragilis*, *E. coli*, *Enterococcus faecalis*, and *Streptococcus gallolyticus* are independently associated with CRC in several combinations and systematic examinations. Metagenomic analysis revealed that gut microbiota associated with CRC, henceforth named CRC microbiota, consist of an abundance of species, a reduced plethora of *Roseburia*, and an enhanced myriad of procarcinogenic bacterial communities like Bacteroides, *Escherichia*, *Fusobacteria*, and *Porphyromonas* (Yu et al. 2017).

Recently, it was detected that intestinal bacteria could stimulate the development of CRC through chronic inflammation initiation, biosynthesis of genotoxin (meddle with the regulation of cell cycle), heterocyclic amine stimulation, or toxic metabolite synthesis of carcinogenic elements of pro-diet (Candela et al. 2014). Chronic inflammation is connected with the risk of evolving cancer and does through causing mutations, cell proliferation, and provoking angiogenesis or apoptosis inhibition (Medzhitov 2008; Grivennikov and Karin 2010). The microbiota dysbiosis benefits opportunistic pathogens that stimulate innate and adaptive immune system components, and bacterial shift, which results in chronic inflammation (Ivanov et al. 2009b). The commensal bacteria stimulate the innate immune system. As a result, dendritic cells, macrophages, and NK cells enhance the production of pro-inflammatory cytokines like TNF-α, IL-23, IL-12, and INFγ, with consequent stimulation of adaptive immune cells, including B cells, T cells, lymphocytes, and other mediators of inflammation (Keku et al. 2015). The inflammatory reaction to commensal bacteria is the stimulation of NF-κB transcription factor and (signal

transducer and activator of transcription) STAT3 in epithelial cells (Greten et al. 2004; Guarner 2006; Hooper et al. 2014; Tian et al. 2003), the production of nitrogen and reactive oxygen species resulting in oxidative stress, damage of DNA, and the progression of CRC. In addition, colonic polyposis is linked with large microbial density compiled inside polyps that induce local inflammatory reactions. The development of polyps and the density of microorganisms may be inhibited through IL-10, a derivative of T cells and Tregs (Dennis et al. 2013). Therefore, it is concluded that the modulation of normal homeostasis among microbiota and host is important for inflammation and the subsequent alterations which cause colon carcinogenesis.

In the interaction between host and microbiota, metabolism is an essential factor. The microbial metagenome encrypts genes that digest more dietary components and host compounds like bile acids. The fecal bile acids increase through a high-fat diet, provoking their enterohepatic circulation and production. The 7α-dehydroxylating bacteria turn colonic initial bile acids into secondary bile acids that are cytotoxic to gut epithelial cells in animal models (Ridlon et al. 2006; Cheng and Raufman 2005). This conversion enhances these secondary bile acids' hydrophilicity (de Giorgio and Blandizzi 2010). Consuming animal protein and a high-fat diet increases the number of secondary bile acids like lithocholic acid, cholic acid, and deoxycholic acid, which causes a higher CRC risk. The deoxycholic acid damages the tract of the mucosa intestine, causes DNA damage, creates genomic instability, and assists the development of tumors. This process might influence bile acids' influence on the colon's carcinogenesis (Rubin et al. 2012).

In contrast, people with a low-fat diet are also affected by CRC, and the risk is through various factors like host health, genetic predisposition, and luminal interplay. Studies determined that CRC cases contained reduced butyrate-producing bacteria *F. prausnitzii*, *Eubacterium rectale*, and increased *Enterococcus faecalis*. Therefore, it is concluded that the colonic bacterial community is a factor that causes CRC.

Furthermore, *B. fragilis*, an enterotoxigenic strain, colonizes the mucosa of adults in an asymptomatic process. However, in a few cases, *these strains release B. fragilis toxin (BFT)*, which induces inflammatory diarrhea. The *B. fragilis* toxin stimulates NF-κB results in the expression of cytokines, which assist in mucosa inflammation (Sears 2009). Therefore, BFT is established as one of the major toxins in the progression of CRC; moreover, in CRC individuals, toxins are transcribed in tumors derived from *Shigella flexneri*, *E. coli*, and *Salmonella enterica*. The data indicate that enterobacterial toxins involve in tumorigenesis (Schwabe and Wang 2012).

The composition and activities of the intestinal microbiota are majorly affected by diet (Duncan et al. 2007). The colonic bacteria produce SCFAs like butyrate, which inhibits CRC progression, prevents histone deacetylases in colonocytes, and induces apoptosis in CRC cell lines (Leonel and Alvarez-Leite 2012; Zhang et al. 2010). Butyrate also stimulates the functions of the large intestine and prevents the growth of pathogens. In addition, butyrate and propionate were exhibited to alter colonic regulatory T cells and utilize an effective anti-inflammatory impact in

Table 3.3 Pathogenetic mechanism of bacteria linked with CRC in murine models

Bacteria	Pathogenetic mechanism	Association with murine model	Reference
Bacteroides fragilis	STAT3 activation; induction of Th-17 immune response IL-1 production; E-cadherin cleavage; stimulation of catenin signaling	Enterotoxigenic *B. fragilis* (ETBF) augments spontaneous colon cancer in multiple intestinal neoplasia (min) mice	Wu et al. (2009); Toprak et al. (2006)
Bacteroides vulgates	Stimulation of MyD88-dependent signaling NF-kB activation	Mono-association of AOM-IL10/ mice lead to mild colorectal tumorigenesis	Uronis et al. (2009)
Enterococcus faecalis	Production of ROS and DNA damage	Stimulates adenocarcinoma in IL-10 KO mice	Balamurugan et al. (2008)
Escherichia coli	Intracellular colonization	*E. coli* NC101 promotes invasive carcinoma in AOM-IL10/ mice; *E. coli* 11G5 enhances colonic polyps in multiple intestinal neoplasia (min) mice	Bonnet et al. (2014)

animal models (Chen et al. 2013). Research studies demonstrated that a fiber-containing diet affects the production of SCFAs (Tomasello et al. 2014). It is concluded that a high-fiber diet increases SCFAs production, with a subsequent decrease in intestinal pH that benefits fermentation in the colon, inhibits pathogen colonization, and reduces the absorption of carcinogen (Macfarlane and Macfarlane 2012) therefore decreasing the risk of CRC (Keku et al. 2015). Different pathogenic mechanisms linked with colorectal cancer are listed in Table 3.3.

3.4.3 Obesity

Obesity is a global condition that is likely accelerating its prevalence worldwide. It affected approximately 107.7 million young children and 603.7 million adults worldwide, and over 60% of fatality is associated with excess body mass index (BMI) (Afshin et al. 2017). Obesity is strongly related to numerous antagonistic comorbidities, such as cardiovascular disease, cancer, and type 2 diabetes mellitus. Obesity is recognized as a complex and multifactorial disorder primarily derivable to peril components of genetic history, lifestyle, and habitat (Hruby and Hu 2015). Over the last decades, the connection and induced role enacted through gut microbiota and obesity have been an astounding discovery. The gut microbiota of mice and humans is dominated by numerous bacterial microbiota containing Bacteroidetes, Firmicutes, and Actinobacteria. The initial observation exhibited distinctive gut microbial configuration in genetically obese (ob/ob) mice correlated to lean (ob/+) and wild (+/+) offsprings in a context of similar polysaccharide-enriched diet (Ley et al. 2005) through epitomizing the decreased plethora of Bacteroidetes and enhanced Firmicutes in obese patients. To characterize the impacts of gut

microbiota from genetic alterations, Turnbaugh and co-workers relocated lean and obese microbiota to germfree mice; consequently, more enhancements in total body fat in recipients colonized by microbiota of obese were observed when correlated to lean microbiota (Turnbaugh et al. 2006). The malfunction of a gut ecosystem that leads to reduced microbiota certainty was linked with IBD and obesity (Qin et al. 2010; Turnbaugh et al. 2009). The initial observations on the association between the gut microbiota and obesity have revealed enhanced Firmicutes number, though a decrease in the number of Bacteroidetes in both humans and mice affected obesity when correlated with lean individuals (Furet et al. 2010). Fascinatingly, these changes can be reversed through weight loss through dietary habits. In the selection of microbiota, the immune system is also considered pivotal. The mice models with unusual TLR signaling or express bactericidal reactive oxygen microbes have exalted antibody serum titers to counteract one's commensal bacteria (Slack et al. 2009). The enriched serum titers are needed to retain the host's and gut microbiota's commensal association. The deficiency of TLRs in mutant mice showed a modified gut microbial composition. The deficiency of TLR-5 mice promotes obesity, metabolic disorders, and inflammation.

The gut microbiota of mice has an enhanced potential to harvest energy from the gut when correlated to their counterparts of germfree mice (Wostmann et al. 1983). Metagenomic gut microbiota studies in obese human and mouse models have identified enhanced carbohydrate fermentation ability (Turnbaugh et al. 2009). This transformation enhances the SCFAs production in the host to enhance the energy harvest. The SCFAs have been suggested to attach to certain GPC receptors such as GPR41, GPR43, FFAR2, and FFAR3, which could improve the nutrient consumption and/or progression of adipose tissue mass. The clinical analyses performed in mice with insufficient GPR41 proposed that the stimulation of GPR41 through SCFAs is responsible for the secretion of PYY gut hormone. Despite this, the mice with abundant expression of GPR43 are fed an obesogenic that enhances the propagation of adipocytes and prevents lipolysis in adipocytes. The mice with GPR43 deficiency are treated with enriched carbohydrates and an enriched fat diet containing a meager body mass and a myriad lean mass correlated with mice of wild type (Bjursell et al. 2011). In addition, the drastic modulations in the composition of gut microbiota, which appear aftermath of medication with antibiotics, can act defense against glucose sensitivity, obesity, and insulin resistance stimulated through enriched fat and a free carbohydrate diet (Cani et al. 2008). According to a recent hypothesis, the gut microbiota can retain the host's metabolic homeostasis. Metabolic disorders like T2DM and obesity are connected with low-level inflammation and modified microbial composition; a microbial strain might enact as a provoking factor in the progression of DM, obesity, as well as inflammation stimulated by a fat-enriched diet.

Low-level metabolic inflammation is considered a pivotal component of metabolic disorders. Numerous analyses illustrated that the metabolic system is unified with an enhanced pro-inflammatory cytokine-like TNF-α, common obesity-associated inflammation, and insulin resistance. Lipopolysaccharides (LPS) endotoxin, an important factor in Gram-negative bacterial cell walls such as Bacteroidetes,

enhances the progression of adipose tissues, affecting insulin resistance and inflammation. LPS also acts as a stimulating factor of fat and enriches diet-activated metabolic disorders. However, metabolic endotoxemia provokes the production of TNF-α, IL-1, and IL-6. The research studies determined that metabolic endotoxemia exists because of the alterations in intestinal microbiota due to antibiotic medication that drastically decreased the native intestinal microbiota and reestablished the common plasma LPS values in the fat-enriched diet fed in mice models. Antibiotic medication suggests that bacteria in the gut affected by antibiotic consumption regulate intestinal penetrability; metabolic endotoxemia occurs. The deficiency of TLR4 (considered as LPS) is defensive against obesity from visceral and subcutaneous adipose tissue development, glucose resistance stimulated by a fat-enriched diet, and the endoplasmic reticulum stress is the major organ for digestion of lipids and glucose.

3.4.4 Diabetes

Genetic background, diet, and environmental conditions influence the gut microbial community. Any significant deviation of these factors influences the apparent habitat alterations. It is significantly stable in middle-aged humans. However, there is a high number of notable gut microbiota alterations that have been in interindividuals. The surfeit of biological reactions regulates with the assistance of modulated gut microbiota.

3.4.4.1 Type 1 Diabetes Mellitus (T1DM)

T1DM is a perennial autoimmune disorder diagnosed usually at a young age and distinguished by the demolition of immune-mediated responses of insulin formation from the pancreatic β-cells (Lamichhane et al. 2018). The ubiquity of T1DM is increasing globally because of a deficiency of suitable therapeutic procedures. The environmental factors associated with a genetic predisposition are eminent for the progression of T1DM (Battaglia and Atkinson 2015). The initial pathogenesis of T1DM is identified by insulitis, abundance expression of autoantibodies over β-cell antigens observed by decreased insulin production, and demise of β-cells (Battaglia and Atkinson 2015). The definite factors responsible for inducing T1DM pathogenesis are still unknown; moreover, the usual aspect that triggers T1DM is genetic history and habitat (Battaglia and Atkinson 2015). The triggering factors like viral infections, usage of antibiotics, consumption of cow milk proteins at early ages, deficiency in breastfeeding and vitamin D supplement, and disclosure to endocrine disrupting synthesis. The function of gut microbiota can affect intestinal mucosa, such as autoimmunity over β-cells. Clinical studies showed that in T1DM models, reduced Firmicutes and enhanced Bacteroides numbers are identified, exhibiting an association between T1DM and microbiota.

In contrast, the reduced number of Bacteroides and Firmicutes is linked with individuals correlated to lean individuals (Schwiertz et al. 2010). Modifications in microbial composition might occur because of differences in the glucose levels of

host results due to diet and intestinal habitat. However, the definite mechanisms are yet unknown, though these alterations might be connected with the progression of T1DM, as reduced *Bifidobacterium* can impact the gut penetrability and mucosal immune reactions affecting autoimmune responses. The interplay between intestinal microbiota and the host immune system enacts an important role in the growth of T1DM. The immune system cells can perceive the metabolites and analytes of gut microbiota which can alter the role of immune cells, stimulating the development of T1DM pathogenesis.

Similarly, the pancreas also consists of its microbiota, and the modification of pancreatic microbiota is linked with the assistance of intrapancreatic immune reactions and initiation of diabetes in addition to pancreatic cancer and T1DM (Pushalkar et al. 2018). The dysbiosis and functions of gut metabolites can stimulate the immune system's GALT malfunctions, like unusual IgA excretion and reproduction of colonic regulatory T cells (Pabst and Mowat 2012). The microbiota-stimulated deterioration of the immune reactions in GALT can also affect systematic immune reactions.

As discussed above, the intestinal microbiota can be able to control the host immune reactions by certain mechanisms such as through stimulating the innate immune reactions by TLRs as well as through stimulating free fatty acid receptors 2/3 (FFAR) by gut metabolites like SCFAs (acetate, butyrate, and propionate) and lactic acid. Butyrate is recognized as linked with the distinction of endemic T cells into Tregs, although acetate and propionate are familiar to be fundamental for shifting Tregs to the intestine (Scott et al. 2018). Abundance stimulation of TLRs and usually less production of SCFAs, majorly butyrate, are noted to have reactive impacts on T1DM-related autoimmunity and might contribute essential therapeutic marks for the inhibition of T1DM. TLRs are imperative for identifying microbial compounds containing nucleic acids, proteins, and LPS. TLRs can also recognize the endogenous compounds produced from the injured tissues or cells by damage-associated molecular patterns (DAMPs) (Scott et al. 2018). In addition, a few analyses proposed that the TLRs (for instance, TLR 3, 7, and 9) are produced in the pancreas of individuals affected with T1DM. TLR mechanisms modify the transcription factor NF-kB and I kappa B kinase (IKK) complex (Xie et al. 2018). NF-kB also controls inflammatory intercessors like IL-Iβ, the usual stimulus of T1DM pathogenesis (Xie et al. 2018).

3.4.4.2 Type 2 Diabetes Mellitus

Globally, T2DM is a common chronic disease with an escalating predominance in several countries. However, the genetic history of individuals is pivotal, although the environmental aspects, lifestyle, and dietary habits are recognized as fundamental factors in T2DM individuals. An auspicious prospective path could use a symbiotic approach linking gut microbiota and diet to treat T2DM. T2DM is distinguished by the decrease in Firmicutes and an enrichment of Bacteroidetes and Firmicutes ratio due to variations in plasma glucose levels (Graessler et al. 2013; Larsen et al. 2010). In the patients affected with T2DM, obesity is proximately associated. Studies have shown that gut microbiota modifications are not similar between both

category patients. The consumption of a high-fat diet enhances certain microbes in the gut, leading to increased levels of lipopolysaccharides and insulin tolerance. T2DM is a complex metabolic disorder characterized by insulin tolerance, hyperglycemia, and metabolic disruption of blood lipids. The gut microbiota is vital in preventing T2DM by modulating individuals' biological activities and metabolism. T2DM associated with the aberrant intestinal microbial composition initiates moderate inflammation. In T2DM individuals, the gut microbiota contains a decrease in the number of butyrate-expressing bacteria, specifically *Roseburia intestinalis* and *Faecalibacterium prausnitzii*; low-grade dysbiosis and pro-inflammatory habitat with enrichment in production of microbial genes responsible for oxidative stress; decreased genes expression entangled in the synthesis of vitamins; and enhanced serum LPS levels and increase in intestinal penetrability.

Furthermore, the major changes in the gut microbiota linked with T2DM contain a reduction in the levels of Firmicutes and an increase of Bacteroidetes and Proteobacteria (Roager et al. 2017). In T2DM patients, the microbiota contains high-grade levels of pathogens like *Clostridium clostridioformis*, *Bacteroides caccae*, *Clostridium ramosum*, *Clostridium hathewayi*, *E. coli*, *Clostridium symbiosum*, and *Eggerthella* spp. (Karlsson et al. 2013). The Gram-negative bacteria produce LPS, which can induce innate immunity by stimulating the TLRs and expressing inflammatory cytokines.

Moreover, LPS induces the expression of NF-kB and c-Jun-terminal kinase mechanisms; these two ways are associated with the progression of insulin resistance and the lack of insulin signaling in adipocytes, liver, and hypothalamus (Newsholme et al. 2016). The metabolites of gut microbiota, such as SCFAs like acetate, butyrate, and propionate, are responsible for the fermentation of dietary carbohydrates. Acetate and propionate are formed from the *Bacteroidetes* sp. The Firmicutes produce butyrate. Dysbiosis is associated with modifying SCFAs production, whereas butyrate progresses insulin resistance and secretion by activating the expression of GLP-1 and decreasing the adipocyte's inflammation (Ríos-Covián et al. 2016). More prominently, butyrate is pivotal for assisting T2DM symptoms.

3.4.5 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder associated with altered bowel discharges and severe abdomen pain. IBS is a downstream signature disease of gut microbiota dysbiosis. Existing evidence claims that gut dysbiosis is the main reason for IBS. The prevalence of IBS is up to 12% in the general population (Lovell and Ford 2012). Pathogenesis of IBS stems from a disturbance in the gut-brain axis due to psychological stress and visceral hypersensitivity. Microbial distribution in the GI tract of healthy individuals differs from IBS patients (Tap et al. 2017). Beneficial microbial communities reduce in the GI tract of IBS patients (Carroll et al. 2011). In 2017, Botschuijver et al. found a decline in the diversity of beneficial mycobiome (fungal communities) in IBS patients (Botschuijver et al. 2017). The overgrowth of pathogenic bacteria in the small intestine induces the pathogenesis of IBS. Small intestine bacteria overgrowth (SIBO)

triggers clinical obligations such as visceral sensation and poor nutrition uptake (Coelho et al. 2000; Giannella et al. 1974). The correlation between SIBO and IBS is quite intuitive. The lack of diagnostic tools that could detect the markers of SIBO is a big problem in IBS clinical practice. But it is possible to screen and characterize the microbial communities during IBS pathogenesis with metagenomics and culture-independent tools. Understanding the gut microbiome dynamics of healthy and diseased individuals might be achieved by case-control studies with advanced genomic tools. Targeting gut microbes as markers enables the choice of therapy with pharmaceutical or non-pharmaceuticals and nutraceuticals.

3.4.6 Diarrhea

Diarrhea is one of the main clinical manifestations ranging from mild to severe gastrointestinal exacerbations. Diarrheal cases are reported in children under 5 years of age in poor and developing countries (MacGill 2017; Roman et al. 2017). Diarrhea is identified as a frequent discharge of loose bowels with high liquidity, nevertheless, poor hygienic practices, intake of contaminated consumables, and multiple factors (Liu et al. 2012). Pathogen invasion is the main reason for diarrheal infections. Certain pathogens, viz., *Salmonella*, *Campylobacter*, *Shigella*, and *Rotavirus*, are responsible for disturbing the gut ecosystem with their invasive mechanisms (Garthright et al. 1988). Non-typhoid *Salmonella enterica* serovar *Typhimurium* is associated with higher infectivity in dysentery cases. Next to *Salmonella*, *Campylobacter* is the pathogen that severely damages the balance in the gut ecosystem. *Shigella* is another food-borne pathogen that affects the small intestine and cause inflammatory diarrhea. *Shigella* can cause infection even at very low inoculums. *Shigella* invasion occurs through contaminated food and water intake, unhygienic sex practices, and poor sanitation. Besides, protozoans *Giardia* and *Entamoeba histolytica* (amoebic dysentery) and *Rotavirus* are responsible for diarrheal dysbiosis in the gut microbiome. Diarrheal infections can be inflammatory or non-inflammatory. Pathogens invade the GI epithelium and affect the intestine's colon and ileum. In non-inflammatory dysentery, the pathogen directly invades the small intestine and mediates its toxicity (Taylor et al. 2013). Antibiotics and oral rehydration solutions are used as therapeutic practices to treat dysentery damage in the gut. With the beneficial effects and nontoxic microbiome reconstructive properties of probiotics, they are currently being prescribed by doctors to combat these types of GI diseases (Kota et al. 2018).

3.5 Redirecting Gut Microbiome to Modulate Host Immunity and Health

Reconstituting the gut microbiome to its native state is called gut eubiosis. Therapeutic strategies with non-pharmaceutical active ingredients that target the host's gut microbiome to modulate the gut microbiome's composition offered

promising and reliable outcomes in recent preclinical and clinical studies. Similar studies focusing on gut health and host immunity regulation with pre- and probiotics suggested strong and reliable observations toward exploring the gut microbiome as an operational tool for immunometabolic therapy. Prebiotics, probiotics, and some other functional foods which could favor nonpathogenic beneficial microbes in the GI tract to grow are mainly investigated and deeply studied as non-pharmaceutical factors to shape the gut environment by modulating the composition of the intestinal microbiome. Both pre- and probiotics are the better choices for immune and metabolic therapy because of their availability and accuracy. Probiotics and prebiotics used in human consumables are enlisted in Table 3.4. Probiotics are certain nonpathogenic microbes that may be residents of the GI tract. Probiotics alter the proportion of gut microbiome toward beneficial microbes and confer host with several benefits such as resistance to invading pathogenic groups and immunometabolic modulation. Prebiotics are the nutritional factors that help probiotic bacteria to grow. Dietary interventions with non-pharmaceutical factors such as probiotics and prebiotics offer an effective way of therapy to combat various gastrointestinal and non-gastrointestinal metabolic disorders by redirecting the gut microbiome to a native or eubiotic state.

Table 3.4 Mostly used prebiotic and probiotics in human consumables

Probiotics	Organism	Reference
Bacillus	*Bacillus subtilis*, *Bacillus coagulans*, *Bacillus laterosporus*	de Simone (2019)
Bifidobacterium	*Bifidobacterium animalis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium catenulatum*, *Bifidobacterium longum*	
Enterococcus	*Enterococcus faecium*	
Lactobacillus	*Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*	
Saccharomyces	*Saccharomyces boulardii*	
Prebiotics		
Arabinoxylan		Chen and Karboune (2019)
Beta glucans		Velikonja et al. (2019)
Fructooligosaccharides (FOS)		dos Santos et al. (2019)
Galactooligosaccharides (GOS)		Fan et al. (2019)
Inulin		dos Santos et al. (2019)
Isomalto-oligosaccharides (IMO)		Wu et al. (2017)
Lactulose		Zeng et al. (2019)
Polydextrose		Ho et al. (2018)
Xylo-oligosaccharides (XOS)		Madhukumar and Muralikrishna (2012)
Xylo-polysaccharide (XPS)		Costa et al. (2019)

3.6 Conclusions and Future Perspectives

The human body harbors several microbial ecosystems called gut, oral, vaginal, skin, and respiratory microbiomes. Gut microbiota regulates the host immune system, and diversions from normal microbial development such as C-sections, formulated diet, antimicrobial usage, and sterile vaccine in neonates alter the progression of immune system outcomes and possibly predispose entities to several inflammatory disorders after that in life. According to immunological and clinical analysis, it is believed that intestinal microbiota dysbiosis might be a fundamental aspect of various inflammatory diseases. Intestinal dysbiosis decreases beneficial microbes resulting in the progression of several inflammatory responses and immune-interceded diseases. Hence targeting and engineering gut microbiota are an effective therapeutic strategy for immune and metabolic issues. Redirecting the gut microbiota from a dysbiotic to a eubiotic state is the main agenda and algorithm of gut engineering. Prebiotics and probiotics or their derived nutraceuticals alter the gut microbes toward the beneficial microbial communities and suppress the inflammatory responses and immune dysregulation, conferring host with boosted immunity and better health.

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