Gut Microbiome Composition as the Key Factor for Immunomodulation in the Host

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Abstract

Gut microbiota is an intricate assortment of microbes that naturally thrive in the digestive tract of humans and other animals. These microbes are very critical for host development, immunity and nutrition. Ample scientific evidences establish the role of gut microbes in human health and diseases. Especially with respect to host immunity, the interaction is highly interlinked with microbiota influencing the induction, training and function of host immune cells, thereby regulating immune homeostasis. In turn, the immune system has a central role in shaping composition, diversity and distribution of host gut microbiota. When immune system–microbiota alliance is operating optimally, a myriad of health benefits are rendered to the host including protection against pathogens, intact intestinal barrier integrity, immunohomeostasis and others. Any disturbance in this intricate association is strongly associated with immunological dysregulation with aberrant immune responses that result in inflammation and tissue injury and subsequently can cause autoimmunity, allergy and cancer. This clearly reflects interdependence of host immune system and their gut microbiota as well the critical role of immune system–microbiota cross talk in the host health and disease.

Keywords

Microbiota · Innate immunity · Pathogen · Immune system · Immune homeostasis

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7.1 Introduction

The gut microbiome is an intricate multifaceted network of about 100 trillion microbes that constitute about 1000 different species (Gerard 2016). These microbes naturally grow within length and breadth of different parts of the gastrointestinal tract with their immaculate ability to get replenished within a short duration of time. These gut microbes develop very quickly right from birth and just after 2–3 years, a stable gut microbiota composition is established. The composition of these microbes is dependent on age, environmental factors (diet, physical activity, etc.) and pathological conditions. In healthy conditions, the microbial diversity and richness enhance with age attaining the highest complexity during adulthood. Ample investigations have demonstrated the role of gut microbiome in human health, nutrition, disease as well as antibiotic resistance (Kau et al. 2011; Ley 2010; Sommer et al. 2009). Due to the critical association between dysbiosed microbiome and the development and progression of various ailments affecting the gut and other visceral organs, microbiota has become a hot research area, especially to biomedical research teams.

Based on various in vitro and in vivo animal models, it has been conclusively revealed that a balanced microbiota composition is very critical for proper functioning of the individual (Pearce et al. 2018). The composition of gut microbiota does change continuously throughout the growth and development of an individual even under normal circumstance. Importantly, this gut microbial population can be manipulated in a desired manner so as to have a better lifelong health benefits. These microbes include archaea, bacteria, viruses, fungi and others that make an intricate ecosystem along the gastrointestinal tract. The total collection of these microbes along with their respective genomes constitutes the microbiome (Bhat and Kapila 2017). Not only the gastrointestinal tract, microorganisms also colonize other anatomical parts such as oral cavity, urogenital tract, mammary gland, skin, mucosa and respiratory tract, but major contribution is from the microbes present within the gut that harbours the densest microbes collectively called as gut microbiota (Dekaboruah et al. 2020). The total number of these microbes is far more than the total number of host cells reflecting that we are much more bacteria as we are human (Sender et al. 2016). Both the microbe number and diversity are very critical in determining healthy as well as diseased conditions of the body. However, the composition of this microbial community is very much host specific that evolves throughout an individual's lifetime with modulations both due to external and internal factors. Further, each bacterial strain harbours thousands of genes, and hence, the collective bacterial genome is about 100 times more than what the host possesses and therefore has a massive effect on host development and functions. These microbes co-evolve and continue to live in the host. The microbes themselves or their metabolites act as critical environmental stimuli and thus affect host functions. Because of this intricacy and interdependence, gut microbiota is now regarded as a virtual organ of the human body for its role in host health and disease (Bhat and Kapila 2017).

With the development of new tools and technique in recent years, the gut microbiome composition, diversity and individual variations have been extensively explored to know dynamic operations of commensal microbiota, though this research area is still in infancy and comprehensive research efforts are still required to know this critical gut microbiota–host interdependence. Further, the main focus is to determine the different microbial species that are predominant during healthy and unhealthy conditions as well as those species that are present during early and elderly stages of development. The gut microbiota has enormous variations consisting of the abundant Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria, Proteobacteria and Verrucomicrobia with Firmicutes and Bacteroidetes together constituting about 90% of gut microbes (Rinninella et al. 2019). The phylum Firmicutes alone includes more than 200 different genera out of which 95% of total Firmicutes is contributed by *Bacillus*, *Clostridium*, *Lactobacillus*, *Enterococcus* and *Ruminococcus*. The highest microbial density lies in the colon (10^{10}–10^{12}/g) with round about 400 bacterial species. In the lower part of the intestine, mostly anaerobic microbes are found that include *Bacteroides*, bifidobacteria, Fusobacteria and peptostreptococci compared to aerobes and facultative aerobes that include enterobacteria and lactobacilli (Illiano et al. 2020) However, the microbiome composition is never the same, and this complex microbe aggregation changes both due to genetic and environmental factors that may include diet, place of living and exposure to environmental pollution such as toxin, carcinogens and antibiotics (Hasan and Yang 2019). In fact, the microbial composition is used to indicate the healthy or unhealthy status of an individual.

Besides, the gut microbiota is closely involved with numerous aspects of host physiology that includes nutritional status, mental and behavioural patterns, responses to variable stress factors as well as health and disease status of the host (Kho and Lal 2018). The proper execution of various gastrointestinal tract functions that include digestion, absorption as well as protection against colonization by pathogens is largely dependent upon these microbes (Bhat and Kapila 2017). Gut microbes are also essential reservoirs of vitamins like K and B, short-chain fatty acids (SCFAs), cholesterol metabolism as well as digestion of dietary polysaccharides that otherwise will remain un-metabolized. Importantly, gut microbiota is closely linked with the development of the host immune system right from the infancy to the elderly stage. Not only the intestinal mucosal immunity but also the systemic immune systems heavily depend on the host microbiota for their proper development and maturation (Zheng et al. 2020). In fact, various immunological pathologies, notably inflammatory bowel disease, celiac disease (multisystemic autoimmune disorder), inflammatory bowel disease, psoriatic arthritis, atopic eczema and others occur due to changes in gut microbial bacterial diversity and functions (Valdes et al. 2018). Studies have shown the close intimacy between the gut microbiota composition and immune system maturation and development along with associated health complications that could develop due to mismatches in the interactions of these two important components of an individual.

7.2 Interdependence of Gut Microbiota and Host Immune Functions

The gut microbiota and host immune system are two critical host components that largely decide the overall functionality of an individual. Importantly both gut microbiota and the immune system affect the functioning as well as the development of each other. The host coexists with these microbes but simultaneously mount a strong and rapid response to the pathogenic microbes (Pickard et al. 2017). The gut microbial communities co-exist in dynamic relationships with the host through intricate networks of interactions and signals. Investigation has shown the cell surface or cytosolic pattern recognition receptors such as Toll-like receptors (TLR), C-type lectin receptors (CLRs), AIM2-like receptors (ALRs), OAS-like receptors (OLRs) and NOD-like receptors (NLR) mediated interactions between gastrointestinal innate immune system and commensal microbes that are responsible for effective defence mechanisms against pathogenic and non-pathogenic dangers (Strowig et al. 2018). Gut microbiota maintains a proper balance between host self-defence and immune tolerance that ultimately results in homoeostatic conditions within the gut. In addition, a number of metabolites, short-chain fatty acids, polyamines, polyphenols and vitamins are released in the gut with the help of gut microbiota, which also influence the host immune functions (Table 7.1). An imbalanced communication between host immune cells and gut microbiota could therefore have many ill effects on host functions, especially with respect to gut immune functions.

7.2.1 Gut Microbiota-Dependent Immune System Development and Maturation

The human gastrointestinal tract (GIT) is home to a vast and most vivid microbial community called microbiota that has a key role in shaping the integrity of host gut immune functions. In fact, the gut microbiota is closely associated with many developmental aspects of the adaptive immune system as well as innate immunity. As reported previously, the early colonization of host's mucosal surfaces in mammals has a key role in the maturation of host gut immune system (Gensollen et al. 2016). In a recent investigation, it was shown that pregnant women with IBD and their offspring had lower bacterial diversity and altered bacterial composition (Torres et al. 2020). When this altered microbiota was transferred to germ-free mice, they showed immature intestinal immune system maturation with fewer class-switched memory B cells and regulatory T cells in the colon as compared to control women and their babies. The role of microbiota in immune system development can be explored especially using germ-free (GF) and gnotobiotic animals. Using specific receptors such as Toll-like receptors (TLRs), nucleotide-binding oligomerization (NOD)-like receptors (NLRs), C-type lectin receptors and others, immune cell system could sense these microorganisms (Thaiss et al. 2016). This receptor-based interaction with microbial components, like LPS, flagellin, bacterial DNA, etc.,

Table 7.1 Microbiota-dependent host immunomodulation

Microbes/ metabolites/ components	Role in regulation	Consequences	References
Faecalibacterium prausnitzii	Induces high levels of IL-10 and reduces the levels of IL-12 and IFN-γ; therefore, it has anti-inflammatory roles	Lower levels of *F. prausnitzii* were observed in Crohn's disease while levels increased during psoriasis	Codoñer et al. (2018)
Polysaccharide A from *Bacteroides fragilis*	Induces regulatory T cells (Tregs) to produce IL-10, suppresses Th17 cell activity and also protects the host from *Helicobacter hepaticus*-induced colitis	Loss of *Bacteroides* was observed during IBD	Round et al. (2011), Chiu et al. (2014)
Butyrate	Exhibits anti-inflammatory activity by inducing intestinal microbiota to release IL-10	Decrease in butyrate observed in IBD	Singh et al. (2014)
Bacteroides thetaiotaomicron	Reduces the levels of inflammatory cytokines by increasing the nuclear export of the RelA subunit of NF-κB, which is responsible for expression of inflammatory genes	High levels of inflammatory cytokines in inflammatory diseases	Kelly et al. (2004)
Bacterial flagellin	Stimulates ILC3 cells to produce IL-22, which provides defence against various pathogens via inducing the production of anti-microbial proteins	Irregular levels of IL-22 observed in human intestinal mucosa in helminth infection	Leung (2013)
Clostridia	Releases butyrate, stimulates differentiation of colonic T regulatory cells (Treg), which have a role in the suppression of inflammatory and allergic responses	Reduced in IBD in association with low amount of butyrate	Furusawa et al. (2013)

results in a cascade of signalling networks including the activation of transcription factor NF-κB, which results in the release of various chemokines, cytokines and anti-microbial proteins (Francino 2014). Members of the microbial community promote pro- and anti-inflammatory responses in the host, which are critical mediators in the maintenance of immune homeostasis (McDermott and Huffnagle 2014). In a recent investigation, five NF-κB suppressive strains were identified belonging to *Clostridium* clusters IV, XIVa and XV that independently suppressed the secretion of the chemokine IL-8 from blood mononuclear cells and gut epithelial organoids (Giri et al. 2019). These NF-κB suppressive microbes suppressed the cytokine-driven inflammatory responses and endoplasmic reticulum stress in gut epithelial organoids

that was responsible for immunomodulatory effects, suggesting the extrinsic regulator role of microbiome in host immunity.

Investigation has shown that gut microbiota plays an important role in the differentiation of T cells into different types of cells including helper T cells (Th1, Th2 and Th17) or regulatory T cells (Tregs) (Belkaid and Hand 2014). For example, segmented filamentous bacteria promote the development of Th17 cells in the intestine, which secrete IL-17 and IL-22, which increased inflammatory response in the host against pathogenic bacteria such as *C. rodentium* (Ivanov et al. 2009). Several studies explained the role of clostridia in the development of $Foxp3^+$ regulatory cells in the intestine, which are anti-inflammatory in nature (Atarashi et al. 2013). Other members such as *Escherichia*, *Akkermansia*, *Bacteroides*, *Clostridium*, *Lactobacillus* and *Streptococcus* were also found to induce these regulatory cells (Geva-Zatorsky et al. 2017). The microbial composition is also able to regulate the generation of $CD4^+$ and $CD8^+$ T cells, which are activated in viral infections and enhanced anti-tumour immunity (Ichinohe et al. 2011; Tanoue et al. 2019). In addition to the regulation of T cell functioning, gut bacteria also stimulate the migration of macrophages and neutrophils in the intestinal tissues for providing protection against pathogens (Kamada and Núñez 2014). Microbes of the gut regularly stimulate the macrophages for IL-10 production, which can further induce Tregs that control the unregulated development of Th17 cells (Rivollier et al. 2012). Recently identified innate lymphoid cells (ILCs) are mainly dependent on the colonization of microbiota for their proper functioning (Kim and Kim 2016). ILCs comprised cytotoxic and non-cytotoxic cells (ILC1, 2 and 3), and most of the studies defined the role of ILC3 in host–microbiota interactions. These lymphocytes restrict the response of T cells to commensal bacteria and thus promote their colonization. Gut microbes also stimulate innate lymphoid cells 3 (ILC3) that subsequently releases IL-22 which acts as activating factor for the enzyme fucosyltransferase 2 (galactoside 2-α-L-fucosyltransferase 2) that protects from enteric pathogens (Thaiss et al. 2016). The development and function of neutrophils are largely dependent locally as well as systemically upon gastrointestinal microbiota. Further, the gastrointestinal tract microbiota affects the differentiation of T cell populations either into the different helper cells that include Th1, Th2 and Th17 or into regulatory T cells (Tregs) (Francino 2014). Conclusively, it can be said that all branches of the immune system are influenced by the microbiota, reflecting the immense role of these microbes in shaping the host immune system.

7.2.2 Role of the Immune System in Shaping Gut Microbiota Complexity

Just like gut microbes influence the immune system functions, the immune system in turn has a key role in deciding the composition and diversity of gut microbiota. In fact, the major proportion of the immune system, approximately up to 70%, resides in the intestine. The host gut defence system includes a diverse array of mechanisms including the multilayered mucus layer and secreted immunoglobulin (sIgA) along

with the release of a number of anti-microbial peptides that on one side provide the host defence but at the same time keep the microbiota in check and maintain a mutual beneficial relationship with them (Dolle et al. 2016). At the same time, the mucosal immunity fights out the potential danger that could result from microbiota-derived antigens through the production of specific antibodies. The secretory immunoglobulin (sIgA) in particular is known to play a vital role in deciding the microbiota diversity and composition (Pabst and Slack 2020).

The immune system consists of lymphoid organs and immune cells such as macrophages, dendritic cells, neutrophils and natural killer cells. In addition to immune cells, epithelial cells of the gastrointestinal (GI) tract also have an important role in maintaining the integrity of gut functionality (Zhang et al. 2015). They act as a strong physical barrier to pathogens and toxins and also work along with other components of the immune system in defence mechanisms. Underneath the epithelial layer, antigen-presenting cells (APCs) and lymphocytes present in the lamina propria and gut-associated lymphoid tissue (GALT), respectively, are components of the gut immune system that respond in an antigen-specific manner (Takiishi et al. 2017). All components function synergistically to combat the pathogen invasion in mucosal tissue. The GI tract is the first one to interact with external stimuli; the epithelium of the GI tract is regularly exposed to several types of antigens like food components, commensal bacteria, pathogens and toxins. Due to these continuous exposures, it can distinguish between commensal bacteria and pathogens and opposed the colonization of pathogenic organisms in the gut. In addition to its role in defence against pathogenic microorganisms, the immune system also plays an important role in shaping the commensal bacteria, which is beneficial for host health. Bilateral interactions of gut microbiota with the immune system generate a number of immune responses, and reversibly the immune system could sense and differentiate commensal microorganisms and pathogens, thus developing tolerance (Zheng et al. 2020).

A number of interactions between the two are characterized over the years. In particular, the mucus layer in the intestine forms a double layer, which acts as a primary barrier to the host's defence. The outer layer of mucus supports the colonization of microorganisms and provides nutrition to them (Kashyap et al. 2013). Some of the cytokines such as TGF-β and IL-10 released from host immune cells are known to maintain mucosal tolerance and also support the colonization of commensal bacteria through stimulation of secretory IgA and thus contribute to intestinal homeostasis (Lazar et al. 2018). Intestinal cells have a pivotal role in maintaining intestinal homeostasis as these cells express a range of immune receptors on their surface. Previouly, it has beeen reported that NOD1 of epithelial cells is necessary for the secretion of C-C motif chemokine 20 (CCL20) that has key role in the developmemt of isolated lymphoid follicles (IFLs) responsible for the production of antigen-specific intestinal IgA immunoglobulins (Bouskra et al. 2008; Fenton et al. 2020). NRLP6 in epithelial cells encourages the inflammasome-mediated IL-18 production as well as the secretion of mucus by goblet cells, which contribute to homeostatic regulation of host–microbiota interface (Wlodarska et al. 2014). It has also an important role in the regulation of anti-viral immunity (Wang et al. 2015).

The role of the innate immune system in the development of the community of gut microorganisms can be best studied in mice models having immune deficiencies. The host's innate immune system might promote the growth of microbiota during dysbiosis. For example, in the case of intestinal infection, fucosylated proteins of intestinal cells induced by ILC3 provide energy to commensal bacteria (Pickard et al. 2014). Signalling via TLR1 during *Yersinia enterocolitica* infection also has a role in the maintenance of intestinal ecological homeostasis (Kamdar et al. 2016).

7.3 Microbiota Released Metabolite and Immune System Modulation

Not only the gut microbes but their derived metabolites such as short-chain fatty acids, polyamines, polyphenols and others have a significant outcome on the host immune functions as shown in Fig. 7.1. Microbial metabolites interact with the host's immune system by interacting with stromal and epithelial cells. In the case of microbial metabolites, short-chain fatty acids (SCFAs), like butyrate, acetate, propionate, succinate and lactate, are the most studied (Morrison and Preston 2016). These metabolites are produced through the action of gut microbiota by fermenting non-digestible carbohydrates like dietary fibres and resistant starch (Bhat and Kapila 2017). These metabolites can get incorporated in intestinal epithelial cells or can diffuse across the epithelium into the underlying intestinal lamina propria, thus influencing different host's immune system. For example, microbiota-produced butyrate regulates transepithelial fluid transport along with reduction of mucosal inflammation. Butyrate is considered an essential secondary metabolite that has a key role in the development and functioning of several immune cell lineages (Man et al. 2020). Previously, gut microbiota-derived butyrate was observed to impart anti-inflammatory effects in the colon through increased histone acetylation of the Foxp3 (forkhead box P3) locus in naive $CD4^+$ T cells, which subsequently increased Foxp3 expression that stimulates the differentiation of Treg cells (Furusawa et al. 2013). Similarly, butyrate-dependent colonic Treg differentiation was reported in myeloid cells through histone deacetylase inhibition (Arpaia et al. 2013). Further, SCFAs derived from gut commensal bacteria increased the naive $CD4^+$ T cells, Tregs and other immune cell populations.

In addition, microbial metabolism of dietary foods in the gut also produces biologically active polyphenolic compounds and polyamines (Bhat and Kapila 2017). Polyphenolic compounds are transformed into various derivatives of aromatic SCFAs such as phenylacetate and phenylbutyrate through the action of microbes such as *Bacteroides* species, *Clostridium* species, *Eubacterium limosum* and *Eggerthella lenta* and subsequently bring out various health benefits. For example, polyphenol fisetin is reported to modulate immune functions when incubated with human monocytic THP-1 cells through the epigenetic inhibition of the expression of NF-jB genes, IL-6 and TNF-α (Kim et al. 2012). Similarly, polyamines have been reported to exert regulatory functions on immune cells possibly by regulating transcription, protein translation, stress protein responses

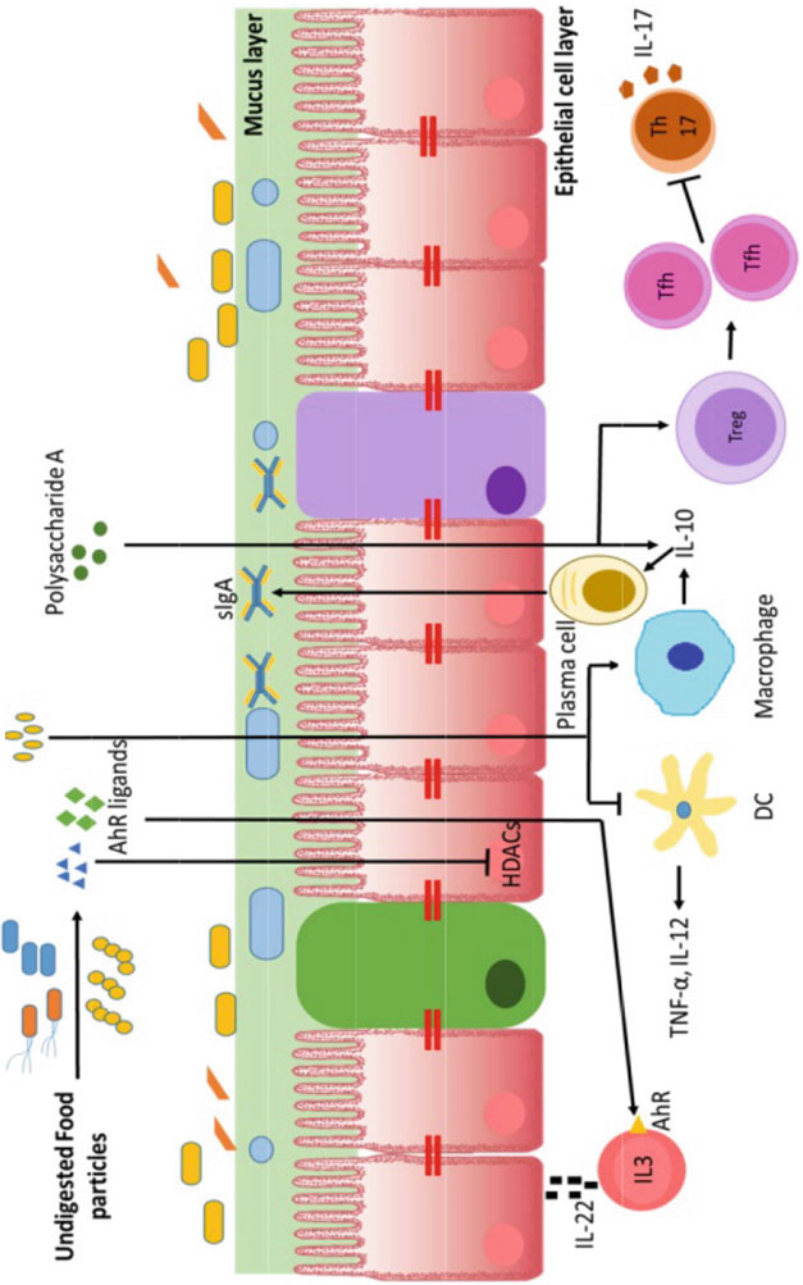

Fig. 7.1 Interdependence of gut microbiota and host immune functions. An array of different bacteria reside in the gut that release a variety of metabolites such as SCFAs (blue, triangle), tryptophan catabolites (green, diamond) and secondary bile acids (yellow, ellipse), which affect the different components of the gut immune system

and cellular metabolism. Polyamines exert anti-inflammatory effects by suppressing inflammatory T cells along with production of cytokines and nitric oxide (NO), thereby having an immunomodulatory effect (Keough et al. 2011).

While the human gut microbiota are suspected to produce diffusible small molecules that modulate host signaling pathways, few of these molecules have been identified. Species of Bacteroides and their relatives, which often comprise. Fifty percent of the gut community, are unusual among bacteria in that their membrane is rich in sphingolipids, a class of signaling molecules that play a key role in inducing apoptosis and modulating the host immune response. Although known for more than three decades, the full repertoire of Bacteroides sphingolipids has not been defined. Here, we use a combination of genetics and chemistry to identify the sphingolipids produced by Bacteroides fragilis NCTC 9343. We constructed a deletion mutant of BF2461, a putative serine palmitoyltransferase whose yeast homolog catalyzes the committed step in sphingolipid biosynthesis. We show that the D2461 mutant is sphingolipid deficient, enabling us to purify and solve the structures of three alkaline-stable lipids present in the wild-type strain but absent from the mutant. The first compound was the known sphingolipid ceramide phosphorylethanolamine, and the second was its corresponding dihydroceramide base. Unexpectedly, the third compound was the glycosphingolipid a-galactosylceramide (a-GalCerBf), which is structurally related to a sponge-derived sphingolipid (a-GalCer, KRN7000) that is the prototypical agonist of CD1d-restricted natural killer T (iNKT) cells. We demonstrate that a-GalCer Bf has similar immunological properties to KRN7000: it binds to CD1d and activates both mouse and human iNKT cells both in vitro and in vivo. Thus, our study reveals BF2461 as the first known member of the Bacteroides sphingolipid pathway, and it indicates that the committed steps of the Bacteroides and eukaryotic sphingolipid pathways are identical. Moreover, our data suggest that some Bacteroides sphingolipids might influence host immune homeostasis. While the human gut microbiota are suspected to produce diffusible small molecules that modulate host signaling pathways, few of these molecules have been identified. Species of Bacteroides and their relatives, which often comprise. Fifty percent of the gut community, are unusual among bacteria in that their membrane is rich in sphingolipids, a class of signaling molecules that play a key role in inducing apoptosis and modulating the host immune response. Although known for more than three decades, the full repertoire of Bacteroides sphingolipids has not been defined. Here, we use a combination of genetics and chemistry to identify the sphingolipids produced by Bacteroides fragilis NCTC 9343. We constructed a deletion mutant of BF2461, a putative serine palmitoyltransferase whose yeast homolog catalyzes the committed step in sphingolipid biosynthesis. We show that the D2461 mutant is sphingolipid deficient, enabling us to purify and solve the structures of three alkaline-stable lipids present in the wild-type strain but absent from the mutant. The first compound was the known sphingolipid ceramide phosphorylethanolamine, and the second was its corresponding dihydroceramide base. Unexpectedly, the third compound was the glycosphingolipid a-galactosylceramide (a-GalCer Bf), which is structurally related to a sponge-derived sphingolipid (a-GalCer, KRN7000) that is the prototypical

agonist of CD1d-restricted natural killer T (iNKT) cells. We demonstrate that a-GalCer Bf has similar immunological properties to KRN7000: it binds to CD1d and activates both mouse and human iNKT cells both in vitro and in vivo. Thus, our study reveals BF2461 as the first known member of the Bacteroides sphingolipid pathway, and it indicates that the committed steps of the Bacteroides and eukaryotic sphingolipid pathways are identical. Moreover, our data suggest that some Bacteroides sphingolipids might influence host immune homeostasis.

The glycosphingolipid α-galactosylceramide (αGalCer) derived from human gut microbe *Bacteroides* and their relatives serves as an important class of signalling molecules that have a key role in inducing cellular apoptosis and modulating the host immune response (Von Gerichten et al. 2019). It was reported that α-galactosylceramide (αGalCer) binds to CD1d and activates both mouse and human invariant natural killer T cells both in vitro and in vivo, suggesting the role of *Bacteroides* sphingolipids in influencing host immune homeostasis. Further, it was noticed that when α-galactosylceramide was presented to cluster of differentiation 1d (CD1d) receptors on antigen-presenting cells, it was observed to efficiently modulate immune responses against tumours, microbial and viral infections and autoimmune diseases. Interestingly, decreased αGalCer production was observed in mice when gut microbiota composition was altered due to colitis and influenza A virus infection. Previously, α-galactosylceramide was also found to diminish inflammation of the intestine in mice colitis model, which subsequently maintained intestinal homeostasis (An et al. 2014). Collectively, these studies demonstrated the critical role of microbiota-derived glycosphingolipid αGalCer in maintaining gut homeostasis, thereby having a key role in mediating local and systemic immune responses.

The microbial community is also a source of secondary bile acids having anti-inflammatory properties and is found to repress the production of tumour necrosis factor (TNF)-α and IL-12 from dendritic cells in addition to increasing the production of IL-10 from macrophages (Fiorucci et al. 2018). One of the tryptophan metabolites, indole-3-aldehyde, acts as ligands for the host receptors such as aryl hydrocarbon receptor (AhR), which enhance the transcription of IL-22, which plays a critical *role* in antibacterial immunity and mediates host defence through the mucosal barrier (Zelante et al. 2013). Other than these metabolites, cell wall components such as polysaccharide A (PSA) from *Bacteroides* species are responsible for the induction of Tregs and production of anti-inflammatory interleukin, IL-10, which are known as major contributors to the maintenance of immune homeostasis (Round and Mazmanian 2010). Similarly, the vitamin A lipid metabolite retinoic acid has been reported to maintain the balance between pro-inflammatory and anti-inflammatory immune responses. Further, it was found that retinoic acid deficiency was found to affect both the composition of the microbiota and immune system function that subsequently resulted in the decreased number of T helper 17 (T_H17) cells (Cha et al. 2010).

7.4 Mechanistic View of Host Innate Immune System and Microbiota Interaction

After understanding the intimate associations between gut microbes and host immune functions, it is very exciting to know about these cellular and molecular mechanisms responsible for these complex pathways. Though the mechanisms involved in the interaction of gut microbiota and host immune cells are not fully explored yet, it believed that these interactions are regulated both at transcriptional and epigenetic levels. Regarding molecular studies, several genes involved in the absorption of nutrients, gut barrier functionality, intestinal immunity and metabolism of xenobiotics are studied over the years to exploit the interactions of the immune system with commensals. The transcription programming of these genes mainly depends upon the sensing of microbial components by intestinal cells (Sommer et al. 2015). These components regulate the expression of the above genes through the regulation of ubiquitin signalling and translocation of p65 transcriptional factor to activate NF-κB inflammatory pathway and also via vesicular trafficking (Thaiss et al. 2016).

Besides transcriptional regulation, host–microbiota interactions are also studied by means of epigenetic modifications. Interactions of cells with microbes could bring changes in the chromatin structure, which further affects the chromatin accessibility to transcriptional factors. These epigenetic events might affect the transcriptional programming of the cells. Takiishi et al. (2017) studied the role of commensal bacteria on the host's innate immune system via the epigenetic pathways. High levels of methylation on the promoter region of TLR4 in colonized mice suggested that commensal bacteria regulated the immune system by suppressing the PRRs. Deletion of histone deacetylase (HDAC3) from intestinal cells resulted in damage to the integrity of the intestinal barrier (Alenghat et al. 2013). Similarly, gut microbiota-dependent epigenetic regulations have been reported to regulate the development of various types of immune cells including $CD4^+$ T cells, Tregs and other immune cells (Alenghat and Artis 2014). Microbiota-derived metabolites such as short-chain fatty acids, polyamines and polyphenols affect the host gut functions including immune functions through epigenetic modulations involving DNA methylation and demethylation, histone acetylation and deacetylation as well as RNA interference (Bhat and Kapila 2017).

7.5 Consequences of Mismatched Interaction Between Gut Microbiota and Immune Cells

From investigation, it is quite obvious that balanced gut microbiota composition is very critical for the overall functioning of an individual. Alterations in interactions of the immune system and gut microbiota because of perturbation in gut microbiota composition might result in faulty functions of the immune system, which could further result in autoimmune and inflammatory diseases. The most common inflammatory diseases due to dysregulation of the microbiota-immune system are

inflammatory bowel disorders including inflammatory bowel disease and ulcerative colitis (UC), while autoimmune diseases include type 1 diabetes, multiple sclerosis (MS) and rheumatoid arthritis (Gianchecchi and Fierabracci 2019).

In a recent investigation, it was reported that differential microbiota composition exists in the small intestine of healthy and unhealthy children with inflammatory bowel disease (IBD) symptoms (Rapozo et al. 2017). Microbial investigation revealed that the children with IBD had decreased total microbial counts of *Collinsella*, *Lactobacillus*, *Bacillus*, Firmicutes, Actinobacteria and Bacteroidetes (Krogius-Kurikka et al. 2009). The dysbiosed intestinal microbe composition makes these children more susceptible to malabsorption of micronutrient resulting in the depletion of essential nutrients within their body, reflecting the interdependence of gut microbiota and host functions. In fact, dysbiosed gut microbiota is associated with the progression of metabolic disorders like obesity, type 2 diabetes mellitus (T2DM), cardiovascular diseases and cancer (Li et al. 2019). Previous investigation has showed the difference in the composition of gut microbiome even between twins, which was later found to be related with the development of obese conditions within one individual than the other (Harley and Karp 2012).

During the development of inflammatory bowel disease (IBD), a constant decrease of microbes belonging to *Faecalibacterium*, *Clostridium* and *Eubacterium* species in contrast to a consistent increase in members of Enterobacteriaceae, *Ruminococcus gnavus* and *Fusobacterium nucleatum* was observed (Brown et al. 2019). In addition to these microbes, loss of PSA and sphingolipids producing *Bacteroides* during IBD further hampers the immune homeostasis (Chiu et al. 2014). In the case of autoimmune disease, MS and a low count of *Bacteroides* and *Faecalibacterium* are also observed (Miyake et al. 2015). Further, it has been found that development of type 1 diabetes is correlated with high abundance of intestinal bacteroids and lower numbers of Clostridiales (Giongo et al. 2011). Alterations in microbiota in RA are mostly associated with an increase in *Prevotella* species, which subsequently enhance the sensitivity for chemically induced colitis and can further contribute to inflammatory diseases (Maeda et al. 2016). In diseased conditions, activities of both innate and adaptive immune cells are debited from their normal functions, especially T cells. T helper (Th) and natural killer T (NKT) cells are known to further contribute to maintaining the inflammation.

7.6 Combating Mismatched Gut Microbiota and Immune System Interactions

Gastrointestinal disorders are mainly associated with alterations in gut microbiota. Therefore, restoration of normal gut microbiota could be one critical step in combating the problems associated with the gut or other visceral organs. At present, faecal microbial transplantation (FMT), that is, a process of transferring faeces from a healthy person to the intestine of the person having gut disorders, is very popular to mediate intestinal homeostasis. The consumption of probiotics, which are defined as live microorganisms, when consumed in adequate amounts, confers benefits to the

host and could be one way to restore these mismatched interactions. These probiotic microbes have been reported to have ample health benefits, especially with reference to intestinal homeostasis in addition to their prophylactic and therapeutic effects in various disease models. However, probiotics have strain-specific effects, and hence, it is very imperative to decide the specific microbes for combating microbiota host mismatches. The combination of these proved to be more effective in the treatment of diseases in comparison to a single strain (Kim et al. 2017).

7.7 Future Perspectives

To know the precise mechanism involved in microbiota, dependent host immune modulation needs to be explored. Epigenetic mechanisms appeared to have a critical effect in mediation of the host gut microbiota immune system modulation but are still in infancy and need to be elucidated further. Detailed investigations involved in host–microbiome interactions could become a suitable target for investigators to ponder upon for coming years.

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