Impact of gut microbiota on immune system

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ABSTRACT
The commensal microflora collection known as microbiota has an essential role in maintaining the host’s physiological homeostasis. The microbiota has a vital role in induction and regulation of local and systemic immune responses. On the other hand, the immune system involves maintaining microbiota compositions. Optimal microbiota-immune system cross-talk is essential for protective responses to pathogens and immune tolerance to self and harmless environmental antigens. Any change in this symbiotic relationship may cause susceptibility to diseases. The association of various cancers and autoimmune diseases with microbiota has been proven. Here we review the interaction of immune responses to gut microbiota, focusing on innate and adaptive immune system and disease susceptibility.

KEYWORDS
microbiota, immune system, dysbiosis

INTRODUCTION

The microbiota includes a wide variety of microorganisms (i.e., bacteria, viruses, protozoa, fungi, and archaea) that reside inside the body spaces of every individual as well as the genes encoded by them [1]. The symbiotic interactions between the microbiota and the host are essential for maintaining physiological homeostasis, response to the environmental changes, and survival in the host. Meanwhile, the microbiota composition can also affect systemic functions, including metabolism, energy balance [2], immunity, and inflammation [3]. Host genetics, such as genetic variations in immunity-related pathways, can impact the microbiota’s composition at various anatomical sites [4]. The host’s lifestyle, including the diet and consumption of antibiotics or other drugs, and even exposure to the natural environment, can play essential roles in the microbiota composition [5].

The immune system consists of multiple cells and molecules in complex networks of innate and adaptive immunity that plays a vital role in host defense against foreign pathogens. The immune system has a symbiotic relationship with the microbiota, which is essential for maintaining the body’s homeostasis. These relationships are required for the proper functioning of the host immunity in order not only to maintain tolerance to microbiota but also to prevent over-exploitation of host resources [6]. Moreover, microbiota plays a fundamental role in regulating the immune system by contributing to the immune system’s training and functional tuning [7]. Change in microbiota composition (dysbiosis) may cause impairment of host-microbiome symbiosis or alterations of the immune system that increase susceptibility to pathogen and aberrant immune responses [6].

Microbial metabolites produced either directly by commensal bacteria or by the dietary material’s metabolism may impact gut homeostasis and modulate the immune responses.
Unlike microbiota, the bacterial-derived metabolites can enter the peripheral circulation and cause systemic effects. Some metabolites such as short-chain fatty acids (SCFAs) and indoles have a protective effect in the development of diseases, and others, such as trimethylamine N-oxide (TMAO) and 4-ethyl phenyl sulfate (4-EPS), directly drive the susceptibility toward diseases [8]. In this review, we will describe the interaction between microbiota and the immune system. We give an overview of microbiota’s impact on regulating the components of innate and acquired immune systems and the immune system’s role in maintaining microbiota composition.

**MICROBIOTA AND INNATE IMMUNE RECEPTOR INTERACTIONS**

Recognition of microbiota through pattern recognition receptors (PRR) of the innate immune system, such as Toll-Like Receptors (TLRs) and Nod-Like Receptors (NLRs), can play essential roles in microbial colonization. PRRs stand at the interface between microbiota and the immune system, and their signaling can help shape the homeostatic host-microbiota interface.

Deficiency in TLRs signaling adaptor protein (MyD88) leads to the change in microbiota composition. It will increase the bacterial translocation to the mesenteric lymph nodes (e.g. the opportunistic pathogen, Klebsiella pneumoniae) [9]. Flagellin receptor, TLR5, is one of the particular TLRs in the prevention of dysbiosis and diseases associated with intestinal inflammation. Microbial flagellin activates TLR5 on dendritic cells (DC) to produce Interleukin-22 (IL-22), promoting protective pathways in epithelial cells, including the up-regulation of anti-microbial gene expression [10]. The loss of TLR5 results in an increase in flagellated microbes associating with low-grade inflammation [11], metabolic syndrome [12], and colitis [13]. Moreover, the microbiota can contribute to Treg (regulatory T cell)/Th17 (T helper 17) balance in the gut by activating TLRs (especially TLR5), resulting in inflammatory and regulatory responses. Depending on the flagellin concentration, TLR5 increases the forhead box P3 (Foxp3) expression on CD4+ T, or T cell effector function [14]. Although TLR9 (recognized bacterial DNA) is expressed in the endosome of immune cells, it is expressed on apical and basolateral membranes of intestinal epithelial cells (IECs). Engagement of TLR9 with its ligand on the apical or basolateral surface on IECs has different effects on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation. TLR9 signaling in basolateral surfaces is associated with Iκκ degradation and activation of the NF-κB pathway and inflammatory response; in contrast, apical signals accumulate ubiquitinated inhibitor of nuclear factor kappa B (Iκκ) in the cytoplasm and prevent NF-κB activation [15]. Polysaccharide A (PSA) produced by Bacteroides fragilis promotes tolerance and prevents trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice by directed stimulation of TLR2 signaling in Foxp3+ regulatory T cells [16]. It seems that the engagement of TLR with some commensal bacteria or their products trigger regulatory responses, unlike pathogens that induced inflammation. Although several studies have suggested that TLR2 [17], TLR4 [18], and TLR9 [19] can potentially impact the microbiota homeostasis, it seems that TLR signaling does not result in significant changes in the microbiota composition under homeostatic conditions or after recovery from high-dose antibiotic treatment [20].

Another PRRs associated with microbial dysbiosis is NOD-like receptors (NLRs). They detect bacterial peptidoglycan (PG) within the cytoplasm of epithelial cells. After PG binding, the activation of the NF-κB signaling pathway leads to the expression of some genes, including anti-microbial peptides, cytokines, and chemokines [21]. Nucleotide Binding Oligomerization Domain Containing 1 (NOD1)-deficiency impacts microbiota and commensal bacteria, such as Clostridiales, Bacteroides in mice, and expands the smaller group of Enterobacteriaceae to 100-fold [22]. NOD2 expression depends on the presence of commensal bacteria and regulates it at a steady state by suppressing de novo colonization of pathobionts (e.g., Helicobacter hepaticus). The balance between NOD2 and commensal bacteria creates a negative feedback loop, and NOD2 deficiency in mice breaks the homeostasis of microbiota, leading to the development of dysbiosis which makes them susceptible to several immune-mediated intestinal illnesses and colorectal cancer [23]. However, a recent study did not show a significant alteration in intestinal microbiota in NOD-1 and NOD-2 deficient mice [24]. In humans, NOD1 and NOD2 genes are associated with the altered microbiota composition and susceptibility to inflammatory bowel disease (IBD) [25–27].

Multi-protein inflammasomes assemble in the cytosol after detecting of Pathogen-associated molecular pattern molecules (PAMPS) or Damage-associated molecular patterns (DAMPs) and then activate the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. Inflammasomes consist of a NLR protein, the adaptor apoptosis-associated speck-like (ASC) protein, and the effector caspase-1. Upon assembling inflammasomes, caspase-1 becomes active through the auto-cleavage of procaspase-1 that cleaves pro-IL-1 and pro-IL18 to their active forms [28]. NLRP6 (NOD-like receptor family pyrin domain containing 6) is an NLR protein highly expressed in the intestinal epithelial cells (e.g., goblet cells) and participates in the inflammasome formation. NLRP6 has critical roles in maintaining intestinal homeostasis and regulates the intestinal microbiota in the steady-state through IL-18-induced anti-microbial peptide (AMP) secretion [28, 29]. The diminished AMP level in NLRP6-deficient mice results in the microbiota dysbiosis associated with sustainability to colitis, persistent infection, and inflammation-induced colorectal cancer [30]. ASC and caspase-1 deficiencies are associated with dysbiosis characterized by reduced IL-18 levels and expanded representation of the bacterial phyla of Bacteroidetes (Prevotellaceae) and Saccharibacteria (known as TM7). Such deficiencies are associated with developed severe colitis after dextran sodium
sulfate (DSS) administration due to non-physiological lymphocytes’ recruitment to the intestine by chemokine C-C Motif Chemokine Ligand 5 (CCL5) [31]. Lemire et al. used littermate NLRP6−/− and wild-type mice. They showed that NLRP-6 did not impact the gut microbiota composition [32]. In contrast, NLRP-6 deficiency in IL-10−/− genetic background mice that develop spontaneous colitis caused significant differences in microbiota composition, compared to NLRP6+/+ IL-10−/− with littermate control mice [33]. Levy et al. also showed different microbiota composition in Asc−/− and Asc+/+ littermate mice [34]. Therefore, it is difficult to explain the roles of NLRP6 inflammasome in forming the microbiota composition.

MICROBIOTA AND INNATE IMMUNE CELLS INTERACTION

Epithelial cells control the microbiota through the secretion of various anti-microbial factors; such as a-defensins (DEFA), produced by Paneth cells, are effective regulators of microbiota composition. The numbers of IL-17A+ CD4+ T cells in lamina propria are reduced in DEFA-deficient mice, linking to loss of segmented filamentous bacteria (SFB) that could shift the mucosal responses towards a pro-inflammatory phenotype [35]. The decrease in the expression of human defensins Human α-defensin (HD)5 and HD6 by Paneth cells impacts the luminal microbiota and predisposes patients to Crohn’s disease of the ileum [36, 37]. Anti-microbial lectins RegIII (regenerating gene family protein III) is expressed prominently in the Paneth cells ileum. RegIII expression increases in response to the bacterial gut colonization and pathogenic infection, leading to inflammation, killing the Gram-positive bacteria, and limiting the activation of the adaptive immunity. RegIII diffusion is restricted to the mucosal surface. Therefore, it physically separates the microbiota from the epithelial surface. RegIII-deficient mice exhibited increased mucosa-associated Gram-positive bacteria colonization by Bacteroidetes and Firmicutes phyla [38].

Lamina propria macrophages play crucial roles in maintaining intestinal homeostasis and shaping adaptive immunity to microbiota. CX3CR1+ macrophages form an interdigitated network close to the mucosa’s entire vascular lamina propria in the mouse’s small and large intestines in the steady-state. These cells act as a firewall that prevents the translocation of bacteria into the blood. In dysbiosis, an increase in bacteria’s movement from the lamina propria to the bloodstream is associated with a gap between the macrophages in this network [39]. CX3CR1+ macrophages prompt tolerance to intestinal microbiota by IL-10 production and antigen function that restricts the Th1 responses and promotes the generation of Treg cells (Fig. 1A) [40]. Microbiota is involved in the tolerogenic intestinal environment by limiting the traffic of antigen-captured CX3CR1+ macrophages from the luminal to the mesenteric lymph nodes [41]. Butyrate and propionate, SCFAs secreted by commensal bacteria, downregulate the pro-inflammatory cytokines expressions, such as IL-6, TNF, and IL-12 in colonic macrophages through inhibiting the activity of histone deacetylases (HDACs) [42]. Moreover, butyrate activates macrophages through an alternative pathway that promotes M2 phenotype polarization and upregulates the arginase 1 expression [43]. In response to the polyamine desaminotyrosine (DAT) produced by Clostridium orbiscindens in the gut, macrophages trigger type 1 interferon responses and contribute to the protection against viral infections [44].

Microbiota also regulates the production and function of neutrophils. Neutrophils are a heterogeneous population

Fig. 1. Crosstalk between microbiota and innate immune cells. A) Microbiota members induce CX3CR1+ macrophages to produce IL-10 that promotes Treg generation, restricts T helper 1 (TH1) cell responses, and limits these cells’ traffic into MLN. SCFAs, such as Butyrate and propionate, modulate macrophage function by promoting M2-like macrophage polarization through upregulating arginase 1 (ARG1) expression and downregulating pro-inflammatory cytokine production (TNF, IL6, and IL12). B) Bifidobacterium infantis upregulates retinoic acid on CD103+ DCs that promote Treg cell generation. Microbiota components such as Prevotella copri produce succinate, signaling through GPR91 on DCs enhance antigen-specific T cell responses. C) ILC3 is activated by intestinal microbes in several ways; cytokines such as IL-1 and IL-23 produced by APCs and IL-7 from epithelial cells strongly activate these cells, but IL-25 produced by epithelial cells inhibit ILC3s, AhR ligands also directly induce ILC activity. ILC3 produces IL-22 that promotes epithelial cell production of mucins and anti-microbial proteins (RegIIb, RegIIg, S100A8, and S100A9). ILC3 also limits dysbiosis
with different pro-inflammatory activities. Neutrophils receive priming signals from the innate immune receptors, such as TLRs (particularly TLR4 and TLR2), NLRs, and MyD88 signaling pathways, and they become more active by aging. Microbiota depletion is associated with a significant and selective reduction in neutrophils in the circulation and bone marrow, leading to delays in neutrophils aging. Multiple microbiota-derived molecules, such as LPS and peptidoglycan, may be involved in neutrophil aging, leading to the generation of a functionally active subset of neutrophils [45, 46].

Intestinal Dendritic cells (DCs), by sending dendrites outside the epithelium into the gut lumen, directly sample bacteria. These DCs restrict the mesenteric lymph nodes and induce Immunoglobulin A (IgA) and local protective bacteria. These DCs restrict the mesenteric lymph nodes and outside the epithelium into the gut lumen, directly sample production of IL-22 may contribute to the dysbiosis through altered microbiota in IBD patients [54]. IFN-γ (Interferon gamma) and TNF (tumor necrosis factor) produced by T-bet+ ILCs, increase the permeability and translocation of nonpathogenic bacteria across the intestinal epithelial cells [55] (Fig. 1C).

**MICROBIOTA AND ADAPTIVE IMMUNITY INTERACTION**

Similar to innate immunity, the adaptive immune system controls the healthy microbiota composition. Host antibody responses influence the microbiota composition through antibody-mediated immunoselection processes (AMIS) [56]. IgA-secreting B cells play crucial and non-redundant roles in maintaining intestinal homeostasis by barrier defense, agglutination through IgA binding, and entrapment of microbes in mucus. IgA directly targets the colonization of a large proportion of commensal microbes and preferentially targets tissue-associated microbes, such as SFB [57]. IgA also contributes to establishing and maintaining a non-inflammatory host-microbial relationship, for example, reducing the expression of the inflammation-inducing proteins of commensal microbes, such as *Bacteroides thetaiotaomicron*, and regulating the expression of the epitopes by the microbiota (Fig. 2) [58].

Moreover, in IgA-deficient mice, microbes are in close contact with the gut tissue, which may explain their high concentration in LPS serum [59]. IgA-deficient humans exhibit an alteration in the gut microbiota composition, decreasing the overall microbiota diversity. Such patients exhibit relative abundances of specific microbial species, such as Enterobacteriaceae [60]. Furthermore, SCFAs promote both local and systemic B cell differentiation into plasma cells by accelerating the cellular metabolism and upregulation of gene expression. In contrast, branched SCFAs produced by species such as *Clostridium sporogenes* suppressed the IgA responses (Fig. 2) [61].

Recently, a collection of 11 bacterial strains were isolated from feces of healthy human donors that can potentially induce both local and systemic IFN-γ + CD8+ T cells in mice. The mechanism of induction depends on the expression of MHC (Major histocompatibility complex) Ia and the presence of CD103+ DC, and anti-tumor immunity. Metabolites from these strains are also capable of inducing IFN-γ CD8+ T cells that may explain these cells’ systemic induction [62]. Oral administration of SCFAs, especially butyrate, increased the IFN-γ and granzyme B expression and shift IL-17 producing T cells toward Cytotoxic T lymphocytes (CTLs) [63].

Cross-talk between CD4+ T cells and the gut microbiota is crucial for orchestrating the adaptive and innate immunity during homeostasis and inflammation. Activated CD4+ T cells reside in peripheral tissues, such as the gastrointestinal tract, colonized by microorganisms. The gut-resident CD4+ T cells respond to microbial antigens necessary for
and function of CD4+ T cells (Th17) in the intestine is essential to control the microbial invasion; however, these cells must be under the control of specific compensatory mechanisms. Any defect in these mechanisms can cause the activation of a pathogenic form of Th17 cells, which induces chronic inflammation and auto-immune diseases. Microbiota is critical for the induction of Th17 cells. Luminal adenosine 5′-tri phosphate (ATP) derived from commensal bacteria induces a unique subset of DCs (CD70high CD11clow cells) in lamina propria to produce IL-6, TGF-β, and IL-23, leading to the differentiation of Th17 cells [69] (Fig. 3C). SFB attaches to the ileal epithelial cells to induce reactive oxygen species (ROS) and serum amyloid (SAA), which modifies the intestinal environment to induce Th17 cells [70, 71]. Bifidobacterium adolescentis is among several species in the human gut microbiota that can induce Th17 cells in mice's gut, similar to SFB; however, with different activities [72]. Th17 cells induced by different species may reveal distinct functional properties. For example, Candida albicans-specific Th17 can produce IL-17 and IFN-γ, but not IL-10, while Staphylococcus aureus-specific Th17 cells can produce IL-17A and IL-10, but not IFN-γ. This is due to the induction of production of high levels of IL-1β due to C. albicans colonization, which consequently inhibits the IL-10 production in memory Th17 cells [73].

Treg cells play a crucial role in auto-immune diseases, and microbiota species and metabolites induce these cells. Microbiota colonization in germ-free mice causes the activation of colonic Treg cells (Fig. 3D). Failure to activate Treg cells causes the induction of Th17 and Th1 cell responses [74]. Microbial metabolites, such as SCFAs, have an essential role in regulating the T cell differentiation into effector and regulatory T cells. Three SCFAs (i.e., acetate, propionate, and butyrate) are the major fermentation products in healthy adults. Depending on the cytokine milieu, SCFAs, particularly butyrate, can directly induce the T-cell differentiation into Th17, GATA3+, and Foxp3+ Tregs and Thf (T follicular helper) cells) [64].

Colonization of the gut with bacteria and viruses drives Th1, Treg, or Th2 cell response. The exact mechanism for the development of Th1 cells by microbiota is unknown. However, some evidence has suggested that microbiota-induced IFN-γ production can originate from both RORγt+ Th17 cells and polarized T-bet+ Th1 cells [65] (Fig. 3A). In mice following the gut colonization by Klebsiella aeromobilis and K. pneumoniae, interferon-inducible genes are upregulated through CD11b+ CD103+ DC subsets, TLR signaling, and induction of IFN-γ producing Th1 cells [66]. IL-25 produced by specialized epithelial cells (tuft cells) is a crucial signal for the induction of Th2 responses. Colonization of the intestine by helminths, such as Heligmosomoides polygyrus and Trichomonas muris in the area of tuft cells that cause hyperplasia, and release of IL-25, which induce the differentiation toward Th2 cells, and production of IL-4, IL-5, and IL-13 [67, 68] (Fig. 3B).

Th17 cells are not present in germ-free mice and are induced following the gut colonization with commensal microbiota. The presence of IL-17 and IL-22 producing CD4+ T cells (Th17) in the intestine is essential to control the microbial invasion; however, these cells must be under the control of specific compensatory mechanisms. Any defect in these mechanisms can cause the activation of a pathogenic form of Th17 cells, which induces chronic inflammation and auto-immune diseases. Microbiota is critical for the induction of Th17 cells. Luminal adenosine 5′-triphosphate (ATP) derived from commensal bacteria induces a unique subset of DCs (CD70high CD11clow cells) in lamina propria to produce IL-6, TGF-β, and IL-23, leading to the differentiation of Th17 cells [69] (Fig. 3C). SFB attaches to the ileal epithelial cells to induce reactive oxygen species (ROS) and serum amyloid (SAA), which modifies the intestinal environment to induce Th17 cells [70, 71]. Bifidobacterium adolescentis is among several species in the human gut microbiota that can induce Th17 cells in mice's gut, similar to SFB; however, with different activities [72]. Th17 cells induced by different species may reveal distinct functional properties. For example, Candida albicans-specific Th17 can produce IL-17 and IFN-γ, but not IL-10, while Staphylococcus aureus-specific Th17 cells can produce IL-17A and IL-10, but not IFN-γ. This is due to the induction of production of high levels of IL-1β due to C. albicans colonization, which consequently inhibits the IL-10 production in memory Th17 cells [73].

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epithelial or the immune cells that microbes contact first are responsible for regulating the T cell response.

Peyer’s patches (PPs) are the primary sites for T-cell dependent IgA production. In germinal centers (GC) of PPs, B cells are activated by antigens and interact with a subset of CD4\(^+\) T cells, known as T follicular helper cells (Tfh) that guarantee the selection of high-affinity IgA. Tfh cells express high levels of CD40L co-stimulatory molecule, programmed cell death protein 1 (PD1) and OX40, as well as IL-21 and IL-4. PD-1 produced by Tfh interacts mostly with PDL-2 on B cells that modulate the in situ GC interaction (Fig. 3). The properties of Tfh can change in PD-1-deficient mice. These cells express more Bcl6 and less IRF4 (Interferon Regulatory Factor 4) while also producing more IFN-\(\gamma\), TNF but less IL-21. Indeed, B cell selection in PPs is impaired in the absence of PD-1 associated with an increase in the abundance of germinal center and reduced affinity for the maturation of IgA-producing plasma cells. As a result, PD-1 deficiency is associated with a reduction in fecal bacteria coated with IgA and diversity of microbiota composition, characterized by a significant decrease in the number (or absence) of beneficial bacteria (e.g., *Bifidobacterium*), and an increase of Enterobacteriaceae [79]. Another T cell subset in GC is T follicular regulatory cells (Tfr) originated from the...
migrated Foxp3⁺ T cells into PPs and are defined as CXCR5⁺ PD-1⁺ Foxp3⁺ cells. The absence of Tfr cells is associated with an increased number of Tfh cells that exhibit disturbed helper functions, such as the production of different cytokines and an increase in GC B cells that produce polyclonal low-affinity IgA. Bacteria coated with high-affinity IgAs contribute to the maintenance of commensal bacteria rather than their elimination, thus, increasing the diversity and stability of microbiota [80].

CONCLUSION

As described in this review, we discussed cross-talk between microbiota and the immune system. In recent years, attention has been paid to the tissue microenvironment in which the immune response is formed. In this microenvironment, the microbiota can act as a regulator of immune responses. Moreover, the association between dysbiosis and various diseases has been proven. Also, microbiota compositions can impact the success of treatment for a variety of diseases, especially cancer. Our knowledge of these cross-talks between the microbiota and immunity is developing. In this microenvironment, the microbiota and the immune system interact with each other and their effect on the immune system is still unknown. The discovery of pathways and molecules derived from these microbes, including viruses, fungi, and protozoa, to each other and their effect on the immune system is still unknown. The discovery of pathways and molecules derived from microbiota involved in these interactions helps to develop new therapies to control infections and regulate immune responses in cancers and auto-immune diseases. It seems that in addition to paying attention to the host genetics, precision medicine should consider the host-microbiome to choose the most effective treatment. Therefore, interdisciplinary study and collaboration between researchers in various fields (such as nutritionists, geneticists, microbiologists, and immunologists) are essential to understand these cross-talks between the microbiota and immune system.

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