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Review Article

Mechanistic insight into the gut microbiome and its interaction with host immunity and inflammation

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ABSTRACT

The intestinal tract is a host to 100 trillion of microbes that have co-evolved with mammals over the millennia. These commensal organisms are critical to the host survival. The roles that symbiotic microorganisms play in the digestion, absorption, and metabolism of nutrients have been clearly demonstrated. Additionally, commensals are indispensable in regulating host immunity. This is evidenced by the poorly developed gut immune system of germ-free mice, which can be corrected by transplantation of specific commensal bacteria. Recent advances in our understanding of the mechanism of host −microbial interaction have provided the basis for this interaction. This paper reviews some of these key studies, with a specific focus on the effect of the microbiome on the immune organ development, nonspecific immunity, specific immunity, and inflammation.

1. Introduction

The intestinal tract is a complex microecosystem, which contains around 100 trillion microbes of different classes (Cultrone et al., 2015). The largest population of intestinal microbes is located in the large intestine and the distal small intestine, most especially in the colon where the bacteria population is up to 10^{12} CFU/mL (O'Hara and Shanahan, 2006). The bacterial population is very low in the small intestinal sections, especially in the duodenum and the jejunum (Fu et al., 2018), which is due to the low pH reduced by multiple digestive enzymes and the relatively quick motility. At the phylum level, intestinal microbiota mainly includes Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria, and Cyanophyta in *Homo sapiens*, *Mus musculus*, and *Gallus gallus*, and Firmicutes and Bacteroidetes account for 90% of all intestinal microbiota (Meng et al., 2018; Moon et al., 2018). Firmicutes mainly include Gram-positive bacteria such as *Fusobacterium clostridia* and *Streptococcus*, and Bacteroidetes mainly include Gram-negative bacteria such as *Bacteroides thetaiotaomicron* and *Bacteroides ovatus* (Seong et al., 2018; Gibiino et al., 2018). Organisms in the gut include anaerobes, facultative anaerobes, and aerobes. The anaerobes account for 99% of all intestinal microbiota (Sommer and Bäckhed, 2013). Based on their effects on the gut, intestinal microbiota falls into 3 categories (Packey and Sartor, 2009): 1) physiological bacteria — these are the dominant bacteria communities in the intestinal tract and are mostly anaerobes, mainly including *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*; 2) opportunistic pathogens — these are comprised of mostly facultative aerobes and incorporate *Escherichia coli* and *Klebsiella pneumonia* (Cerny et al., 2015); 3) pathogenic bacteria such as *Clostridium perfringens* (Lin et al., 2017).

The embryo gut is sterile in the utero during pregnancy (Xiao et al., 2017). However, microorganisms immediately populate the gastrointestinal tract after the newborn contacting with the external environment to form a stable gut microbial community (Bäckhed et al., 2015). *Bifidobacterium* is one of the earliest colonizers of the gut (Freitas and Hill, 2018). The dynamics of gut microbiome colonization is influenced by the mode of delivery of

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the newborn, postnatal diet, gestational age, hygiene level, and medication (Indrio et al., 2017).

The microbiome evolves with animals over several thousands of years and a symbiotic relationship has been established to ensure the survivals of both the microbes and the host. Gut microbes are involved in digestion and absorption of nutrients. For example, gut microbes play important roles in the nutrient harvest by increasing the host nutrient digestibility through secreting digestive enzymes and enhancing the enzymatic activity (Adorian et al., 2018). Microbiota can produce short-chain fatty acids (SCFA) through the fermentation of food in the gut to supply extra energy to animals (Wang et al., 2017b). Short-chain fatty acids, such as formic acid, acetic acid, propionic acid, butyric acid, and valeric acid, are the organic fatty acids with the number of carbons from 1 to 5 (Gardana et al., 2017). Gut microbes also synthesize and provide critical vitamins that promote the health and the metabolism of the host (Carrizo et al., 2016). Recent studies showed that the gut microbiota is strongly linked to the regulation of the host immunity and inflammation. For example, dietary probiotics promote immunity and reduce inflammatory responses of the host animals (Guo et al., 2017; Khailova et al., 2016). When germ-free animals and conventional animals are infected with the same virus, the immune response in germ-free animals is significantly reduced, accompanied by severe diseases (Ganal et al., 2012). However, the immune response of germ-free animals is rescued through the transplantation of gut microbiota from conventional animals (Ganal et al., 2012).

The gut is one of the largest immune organs in the body (Desselberger, 2018). The intestinal barrier is a multilayer that comprises microbial, chemical, mechanical, and immune barriers and it protects the host against pathogens (Wang et al., 2015). Gut microbiota constitutes the microbial barrier. It suppresses the growth and reproduction of pathogens by competing with them for nutrients and adhesion sites on the host (Jandhyala et al., 2015; Roselli et al., 2017). Commensal microbes also take part in the constitution of the chemical barrier by secreting various substances, such as the bacteriocin, to inhibit pathogens colonization (Kreth et al., 2009). The mechanical barrier includes mucus, physical absorption, fluid dynamic systems, epithelial cells, and tight junctions. Transmembrane proteins, such as claudins, and cytoplasmic proteins, such as the zonula occludens 1 (ZO-1), ZO-2 and ZO-3, take part in the constitution of tight junction (Kim et al., 2018). The gut-associated lymphoid tissue (GALT) and diffuse immune cells are important components to form the immune barrier. Gut-associated lymphoid tissue maintains the homeostasis of host immunity through its ability to sense and scavenge pathogenic bacteria leading to tolerance and prevention of pathological immune response. The establishment of immune tolerance is related to Toll-like receptors (TLR) and nuclear factor kappa-B (NF-κB) signal pathway (Tostanoski et al., 2019; Riemann et al., 2017). Gut microbiome can restrain NF-κB signal pathway by suppressing the ubiquitination of inhibitor of NF-κB to establish the gut immune tolerance (Neish et al., 2000). Meanwhile, the gut microbiome is an important factor to stimulate the maturation of the immune system (Lee-Sarwar et al., 2018). Gut microbiota can influence specific immunity and nonspecific immunity in different ways (Table). This paper reviews key studies that cover the core mechanisms, such as the impact of the gut microbiome on the development of immune organ, nonspecific immunity, specific immunity, and inflammation. These studies provide a theoretical basis for the understanding of how the gut microbiome regulates immunity and inflammation.

2. Gut microbiome and its effect on immune organ maturation

Immune organs are divided into central and peripheral immune organs. The central immune organs, such as the thymus gland, bone marrow, and bursa of Fabricius (one of immune organs in avian species), are the places for immune cells to develop, differentiate, and mature. The peripheral immune organs are the places that immune cell settles down and immune response happens. The peripheral immune organs incorporate the lymph gland, spleen, and mucosa associated lymphoid tissues, which mainly include the GALT. The peripheral immune organs have important functions to keep the balance between immunity and tolerance, and they also are able to induce tolerance under the certain circumstance.

The gut microbiome has a remarkable effect on the development of immune organs. The weight and development of the thymus in germ-free animals are significantly lower than those in conventional animals (Waaij, 1986). The B cell and T cell regions are shrunk in the spleen of the germ-free mouse compared with the conventional mouse, and there is considerable endothelial microvessel hyperplasia in the germ-free mouse compared to the conventional mouse, an indication of immaturity (Macpherson and Harris, 2004). In addition, the structures of the B cell and T cell regions in the spleen and lymph nodes of the germ-free mice are in disorder (Benveniste et al., 1971). The volume and number of cells in the mouse spleen germinal center, an area which includes the B cell germinal center, are smaller in germ-free animals than in conventional animals, which indicates the poor differentiation and maturation of the B cells in germ-free animals (Crabbé et al., 1968). Previous evidence showed that microbiome colonization could change the structure of the intestinal villi and crypt to promote the maturation of gut (Sommer and Bäckhed, 2013). The intestinal epithelium of germ-free animals is poorly developed due to the weakness of vascularization (Hall et al., 2008). Additionally, the epithelium of cecum in germ-free animals is less healthy than that in conventional animals including the thinner intestinal walls, the longer villi, and the narrower crypts (Umesaki et al., 1993). Simultaneously, the lymph nodes of germ-free animals are smaller and the numbers of lymphocytes, plasma cells, T cell receptor, $CD4^+$, and $CD8^+$ T lymphocytes are greatly reduced (Bauer et al., 1963). These abnormalities are capable of being reversed after microorganism colonization (Yanagibashi et al., 2013).

The development of GALT is mediated by the gut microbiome, including the Peyer's patches (PP), the isolated lymphoid follicles (ILF), and the mesenteric lymph nodes (MLN) (Spahn et al., 2015). The PP, the MLN, and the primordial germinal center are smaller in germ-free animals than in conventional animals, and the ILF is immature and the numbers of B and plasma cells are significantly reduced (Macpherson and Harris, 2004; Umesaki et al., 1993). The gut microbiome can promote the growth of the MLN and the PP (Yamashita et al., 2014). Engraftment the gut microbiome from conventional to germ-free animals leads to the recovery of GALT development (Lin and Zhang, 2017). When *Bacillus subtilis* and *Bacillus fragilis* are injected into the abdominal lumen of germ-free rabbits, they can facilitate the growth of GALT and induce the proliferation of B cells (Rhee et al., 2004). Previous studies showed that, although lymphoid tissues such as the PP and the MLN could be formed under a sterile environment during fetal growth, the full development of the PP and the MLN was only facilitated through the interaction with the microbiome after birth (Renz et al., 2012), and the microbiome was critically needed for the development of the ILF (Pabst et al., 2006).

Table
The influence and mechanism of gut microbiota on immune responses.

Gut microbiota	Mechanism	Function
Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii	Promote mucus secretion	Facilitate goblet cell differentiation (Wrzosek et al., 2013)
Firmicutes	Butyric acid	Promote epithelial barrier function: 1) regulate the development of intestinal macrophages (Koh et al., 2016); 2) stimulate the expression level of *NLRC3* (Cheng et al., 2018); 3) repress the claudin-2 protein expression depending on *IL-10RA* (Zheng et al., 2017)
Lactobacillus	Enhance the secretion of TNF-α and IL-12 in dendritic cells	Strengthen the body antiviral response (Drakes et al., 2004)
Lactobacillus casei, Bifidobacterium	Increase the concentration of SIgA; Up regulate the expression level of *Foxp3*	Enhance the humoral immunity response (Helgeland et al., 2010) Curtail excessive immune response (Rinaldi et al., 2018)
Bifidobacterium	Stimulate the secretion of IL-1 and IL-6; Reduce the contents of lipopolysaccharide and proinflammatory factor	Enhance humoral immunity response (Zhu et al., 2018); Promote the differentiation of Th cells (Myszka and Klinger, 2014); Alleviate intestinal inflammation (Yan et al., 2019)
Bacillus subtilis	Regulate the differentiation of Tregs and Th17 cells	Keep the balance between Tregs and Th17 cells (Lee et al., 2012)
Bacteroides fragilis	Polysaccharide A	Influence the Th1 immune response (Horai et al., 2017) and accelerate the differentiation of Treg cells (Round et al., 2011)
Segmented filamentous bacteria *Clostridium*	Induce SAA, TGF-β, IL-6, IL-23 secretion Stimulate the secretion of TGF-β, and increase the expression of *Foxp3*	Induce the differentiation of Th17 cell (Ivanov et al., 2009) Induce the proliferation and differentiation of Tregs (Tinoco-Veras et al., 2017)

NLRC3 = nucleotide-binding oligomerization domain-like receptor 3; *IL-10RA* = interleukin 10 receptor α subunit; TNF-α = tumor necrosis factor α; SIgA = secretory immunoglobulin A; *Foxp3* = fork head/winged helix transcription factor p3; Th = T helper; Treg = regulatory T; SAA = serum amyloid protein A; TGF-β = transforming growth factor β.

3. Gut microbiome regulates non-specific host immunity

Non-specific host immunity system is the first line to resist against antigen. It includes organizational barriers (skin barrier, mucous membrane barrier, blood–brain barrier, placental barrier), innate immunocytes, and innate immune molecules. Innate immunocytes include macrophages, neutrophils, natural killer cells, eosinophils, basophils, and membranous cells. Especially, macrophages and neutrophils have the phagocytic function and they can devour pathogen. Innate immune molecules include complement, lysozyme, and interferon (IFN). The activation of non-specific host immunity relies on pattern recognition receptors, which include TLR, nucleotide binding and oligomerization domain like receptors (NLR) (Corridoni et al., 2018). Pattern recognition receptors can recognize the pathogen-associated molecular patterns and activate dendritic cells, macrophages, mastocytes, and innate lymphoid cells (ILC) (Lee et al., 2019). At least 13 different TLR have been identified in animals (Lee et al., 2017). Toll-like receptor 4 is able to recognize lipopolysaccharide (LPS), which is the composition of Gram-negative bacterial cell wall, and to activate the downstream antibacterial signaling (Nighot et al., 2019). A previous study showed that LPS increased the permeability of intestinal epithelial tight junction, which was related to TLR4 and myeloid differential protein 88 (MyD88) pathways (Lee et al., 2017).

D. Van der Waaij et al. raised a concept of colonization resistance (Waaij et al., 1971) by which some obligate anaerobes can form the microbial barrier on the surface of the intestinal epithelium, compete with pathogenic bacteria for attachment sites and nutrients, and restrain their adhesion and colonization (Wang et al., 2002). Gut microbes produce various metabolites such as bacteriocin, SCFA, hydrogen peroxide, antimicrobial peptides, and lysozyme (Sommer and Bäckhed, 2013; Quereda et al., 2017; Wen and Wong, 2017). These substances can suppress and kill the pathogenic bacteria (Kreth et al., 2009). Short-chain fatty acids reduce the pH of the gut and suppress the growth of pathogens. Acetic acid and propionic acid are mainly produced by Bacteroidetes, and butyric acid is mainly produced by Firmicutes (Chang et al., 2014). Mucoprotein (MUC) is secreted by goblet cells and forms the inner and outer mucus layers. Symbiotic bacteria reside in the outer mucus layer and they cannot get across the inside mucus layer, so the contact between bacteria and enterocyte is lessened (Johansson et al., 2013; Hadaidi et al., 2017). The MUC2 is the most abundant MUC in the gut tract and exists in the outer mucus layer. It competes with pathogenic bacteria to bind to the surface receptor and inhibits the pathogen colonization. *Lactobacillus acidophilus* was reported to facilitate the expression of *MUC* (Oh et al., 2017). Simultaneously, gut microbiome can up-regulate the expression of regenerating islet-derived III protein and enhance the resistance of pathogenic bacteria (Cash et al., 2006).

Gut microbiome can enhance the host non-specific immunity by maintaining and strengthening the intestinal barrier function. *B. thetaiotaomicron* and *Faecalibacterium prausnitzii* can promote the mucus secretion of intestinal mucosa and facilitate the goblet cell differentiation (Wrzosek et al., 2013). In addition, *Streptococcus thermophilus* and *L. acidophilus* can accelerate the phosphorylation of tight junction protein in the gut mucosa (Scaldaferri et al., 2012). Butyric acid can promote epithelial barrier function and the underlying mechanism are as follows: 1) regulating the immunological development of intestinal macrophage by suppressing the expression of histone deacetylases (Koh et al., 2016; Chen and Vitetta, 2018); 2) stimulating the expression of *NLRC3* through binding G-protein coupled receptor 43 (Cheng et al., 2018); 3) repressing the expression of claudin-2 protein by depending on interleukin (IL) 10 receptor α subunit (Zheng et al., 2017). Gut microbiome secretes muramyl dipeptides, which can help the lysozyme storing of the Paneth cells (Wang et al., 2017a). Gut microbiome also plays a role in regulating the non-specific immune cell function and the cytokine secretion. Dendritic cells recognize symbiotic bacteria and pathogens to trigger the innate immunity (Mason and Hovius, 2018). Probiotics can up-regulate the expression levels of CD80, CD86, CD40, and major histocompatibility complex II and can facilitate the secretion of 5-hydroxytryptamine in the dendritic cells (Drakes et al., 2004). *Lactobacillus* can strengthen the body antiviral response by enhancing the secretion of tumor necrosis factor α (TNF-α), IFN-γ, and IL-12 in the dendritic cells (Drakes et al., 2004). Gut microbiome increases the development and population of non-specific immune cells. Studies showed that the number of $ROR\gamma t^{+}$ $NKp46^{+}$ $CD127^{+}$ $NK1.1^{-}$ ILC and $ROR\gamma t^{+}$

NKp46^{+} *CD127*$^{+}$ *NK1.1*^{int} ILC decreased significantly in germ-free mice, indicating that microorganism was necessary for the differentiation of innate lymphoid cells (Satoh-Takayama et al., 2008). *E. coli* can increase the number of dendritic cells in germ-free piglets (Haverson et al., 2007).

4. Gut microbiome regulates specific immunity

Specific immunity includes the humoral immunity mediated by B cells and the cell-mediated immunity carried out by T cells. After activating by antigen, B cells can convert to plasma cells and memory B cells, and plasma cells can secrete antibodies. Antibodies as an immunoglobulin incorporate IgA, IgD, IgE, IgG and IgM. T cells can be divided into helper T cells (Th cells), regulatory T cells (Treg cells or Tregs), cytotoxic T cells (Tc cells) and memory T cells. Cytotoxic T cells directly attack target cells and induce the apoptosis of target cells. Helper T cells can help Tc and B cells to play the immune response function by secreting multiple cytokines. Treg cells restrain the immune response. The gut microbiome is involved in the regulation of specific immunity through its effect in the regulation of IgA secretion, activation of T cells (Tanoue et al., 2016), and proliferation of lymphocyte. The quantity of thymus lymphocytes is significantly lower in germ-free mice than in specific pathogen free mice.

4.1. Regulation of humoral immunity by the gut microbiome

Gut microbiome promotes the maturation of B cells, which are involved in the antibody production. The human infant gut is rapidly colonized by *E. coli* and *Bifidobacterium* from 4 to 8 wk after birth, and these microbes significantly increase the number of CD20^{+}CD27^{+} B cells in peripheral blood from 4 to 18 months (Lundell et al., 2012). Gut bacteria also can promote B cell differentiation. Short-chain fatty acids, as the metabolites of gut microbiome, increase the transformation of B cells into antibody-producing cells (Kim et al., 2016). The flagellin of symbiotic strains can induce B cell differentiation through promoting the synthesis of retinoic acid (Mora et al., 2006). Symbiotic strains contact with dendritic cells, activate MyD88 signaling, and promote the differentiation of IgA^{+} B cells through the secretion of transforming growth factor β (TGF-β), chemokines chemokine (C-X-C motif) ligand 13 (CXCL13), and B cell activating factor (Kunisawa et al., 2013). The gut microbiome also influences the number of B cells. The exposure of germ-free mice to conventional mice results in an increase in the number of pro-B cells in the lamina propria of germ-free mice (Wesemann et al., 2013).

Gut microbiome influences the secretion of immunoglobulins to prevent pathogen colonization and enhance immune response. Membrane IgA and secretory immunoglobulin A (SIgA) are 2 types of immunoglobulin and the SIgA plays an important role in the immunologic function. SIgA prevents pathogen adhesion in the gut and promotes the identification and clearance of pathogen and bacterial toxin by combining with them. IgA is secreted by B cells and binds with the antigenic regions of pathogens to neutralize them. The production of IgA is impaired in germ-free animals (Shroff et al., 1995), but the production of IgA, IgG, and IgM is restored with microbial colonization (Laycock et al., 2012; Hansson et al., 2011). The type of bacteria can influence the concentration of antibody. The serum concentrations of IgG and IgM are higher in germ-free pigs colonized by enterohemorrhagic *E. coli* than those in the germ-free pigs colonized by non-pathogenic *E. coli* (Butler et al., 2010). Probiotic strains such as *Lactobacillus casei* and *Bifidobacterium* increase the concentration of SIgA in the gut (Helgeland et al., 2010). The *Bifidobacterium* stimulates immune cells to secrete IL-1 and IL-6. Interleukin-1 promotes the antibody production, whereas IL-6 promotes the maturation and differentiation of B lymphocytes (Zhu et al., 2018). Gut microbiome affects the expression of genes related immunity in the spleen and the Peyer's patches, and the levels of IgA, IgG, and IgM are significantly elevated in conventional mice than in germ-free mice (Hansson et al., 2011).

Gut microbiome has a remarkable influence on the antibody diversity. The antibody diversity of IgA and IgM in GALT of conventional piglets is higher than that of germ-free counterparts (Kassam et al., 2013). Along with an increase of microorganism species in the gut, the antibody diversity of IgA becomes abundant (Lindner et al., 2015). Symbiotic bacteria induce the secretion of cytokines such as TNF, proliferation-induced ligands and TGF-β in the mononuclear phagocytes, and the intestinal epithelial cells (IEC) to promote the type conversion of IgA (Macpherson et al., 2015). Gut microbiome colonization in the germ-free mouse increases the number of recombination activating gene 2 (*RAG2*)$^{+}$ B cells and the expression levels of *RAG1* and *RAG2* in the gut lamina propria to influence the *V(D)J* gene rearrangement, which is the major mechanism of immunoglobulin diversity (De Vos and De Vos, 2012). In addition, the value of Igλ/Igκ increases significantly in the gut lamina propria, indicating that gut microbiome may be involved in an increase in the diversity of B cell receptor (BCR) (Wesemann et al., 2013).

4.2. Gut microbiome regulates cellular immunity

The gut microbiome also regulates the balance of Th cells and Treg cells (Agace and Mccoy, 2017), which are 2 kinds of T cells involved in cell-mediated immunity. Th17 cells are a special kind of CD4^{+} Th cells that regulate the development of autoimmune diseases through the production of inflammatory cytokines such as IL-17A, IL-17F, and IL-22. The microbiome is necessary for the development of Th17 cells and the quantity of Th17 cells is lower in the colon of germ-free animals than in the colon of conventional animals (Ivanov et al., 2008). The gut microbiome regulates the proliferation of Th17 cells through an interaction with TLR (Hall et al., 2008). The maintenance of balance between Th17 cells and Treg cells is very important and this influences the gut immunity and tolerance. *Clostridium* regulates the proliferation and differentiation of Tregs and Th17 cells and increases the quantity of IL-17 secreted by Th17 cells to accelerate the immune response (Molloy et al., 2012). Poly-γ-glutamic acid (γ-PGA) produced by *B. subtilis* can promote the differentiation of Treg cells, but suppress the differentiation of Th17 cells, and also promote the secretion of IL-12 and IL-6 (Lee et al., 2012). *E. coli* colonization in germ-free piglets increases the number of T lymphocytes in the lamina propria (Haverson et al., 2007). The numbers of Th1, Th17, and Treg cells are decreased in mice with enteric dysbacteriosis and accompanies a change in the levels of multiple cytokines such as IL-7, IL-10, IL-22 and IFN-γ (Takiishi et al., 2017). Short-chain fatty acids are produced by gut microbiome can affect the activity of RORγt to maintain the homeostasis of Th cells (Smith et al., 2013). TGF-β, IL-6, IL-21 and IL-23 promote the conversion from Th precursor to Th17 cells. *B. fragilis* accelerates the production of Th cells by promoting the secretion of IL-17 and also influences Th1 immune response through changing the production of bacteria polysaccharide A (Horai et al., 2017). Vitamin D, which is generated by *Bifidobacterium*, can also promote the differentiation of Th cells (Myszka and Klinger, 2014). Studies had also shown that segmented filamentous bacteria (SFB) plays an important role in the Th17 cells development. The number of Th17 cells is lower in the

small intestine lamina propria of mice without SFB than that with SFB, and the number of Th17 cells increase significantly after the SFB colonization (Clarke et al., 2014). Segmented filamentous bacteria induce serum amyloid protein A (SAA) secretion in the small intestine, and SAA can induce the differentiation of Th17 cells by increasing the quantity of TGF-β, IL-6, and IL-23 secreted by dendritic cells (Ivanov et al., 2009).

Gut microbiome also promotes the proliferation and differentiation of Treg cells which regulate immune homeostasis. It is important in the recognition of autoantigens and in the negative control of immune response. The expression of fork head/winged helix transcription factor p3 (*Foxp3*) is lower in the MLN of germ-free mice, and the number of Treg cells is also lower in peripheral lymph node compared with conventional mice (Ostman et al., 2010; Atarashi et al., 2011). The Foxp3 is an important transcription factor which controls the development of Tregs. *Lactobacillus* and *Bifidobacterium* can up-regulate the expression level of *Foxp3* to curtail excessive immune response (Rinaldi et al., 2018). Mechanistically, *Clostridium* stimulates *TGF-β* production and increases the expression of *Foxp3* to induce the proliferation and differentiation of Tregs (Tinoco-Veras et al., 2017). The butyric acid produced by *Clostridium* increases the acetylation level of *Foxp3* promoter to induce a conversion from $CD4^+$ T cells to Tregs (Arpaia et al., 2013). Meanwhile, *TGF-β* has multiple effects of regulating immune responses (Tinoco-Veras et al., 2017). Poly saccharide A (PSA) produced by *B. fragilis* can activate TLR2-MyD88 signaling pathway to accelerate the differentiation of Treg cells (Round et al., 2011).

5. Gut microbiome and inflammation

An inflammation reaction can lead to a tissue damage which is triggered by multi-factors (Skaper et al., 2018). IL-6, TNF-α and IL-1β belong to the pro-inflammatory cytokine, whereas cell permeability proteins, IL-4, IL-10, IL-13 and TGF, belong to the anti-inflammatory cytokines (Sabitha et al., 2019; Reyes-Díaz et al., 2018). They play an important role in regulating the inflammation reaction.

Inflammation is closely related to gut microbiome. Multiple inflammatory diseases are associated with the alteration of intestinal microbiome. The numbers of *Bacteroides*, *Streptococcus*, and *Clostridium* are increased in the gut of autoimmune pancreatitis patients (Hamada et al., 2018). The numbers of *Bacteroides*, *C. leptum*, and *Hemophilus* are decreased, whereas the number of *Lactobacillus salivarius* is increased in the gut of rheumatoid arthritis patients (Zhang et al., 2015). Obesity is regarded as a low-grade inflammation. The gut microbiome diversity in the obesity individuals is lower compared with normal ones along with a decrease in Bacteroidetes and an increase in Actinobacteria. Inflammatory bowel diseases (IBD) are a nonspecific inflammation of the gut. They include ulcerative colitis, Crohn's disease, and indeterminate colitis. Intestinal flora imbalance is identified as the main reason for the IBD (Swidsinski et al., 2010). Lower abundance of *Roseburia* has been associated with a higher incidence of IBD (Imhann et al., 2018). The quantities of Ruminococcaceae and Rikenellaceae are lower in the gut of IBD patients (Imhann et al., 2018). The transplantation of fecal microbiota from mice with IBD to normal mice can induce the *IL-33* secretion from the intestinal mucosa and activate Th2 cells to mediate the immune response which leads to ileitis (Salvo et al., 2016). Presence of *E. coli* has also been confirmed in the intestinal mucosa of IBD patients (Ferla et al., 2004). Toll-like receptors on the surface of epithelial and antigen presenting cells can recognize aforementioned bacteria, activate NF-κB, lead to the transcription of inflammatory gene, and induce the intestinal inflammation (Kinnebrew and Pamer, 2012). However, butyric acid limits the activation of NF-κB and the secretion of IL-12 and TNF-α (Brown et al., 2011; Lewis et al., 2010), an evidence that certain bacteria species producing butyric acid may limit the inflammation in the gut.

Probiotics can prevent IBD. For example, *B. fragilis* can transfer capsular polysaccharide A to dendritic cells through the outer membrane vesicles, and the dendritic cells are able to induce Tregs to secrete IL-10 to prevent or limit IBD. The capsular polysaccharide A can also directly activate TLR2 signal pathway to restrain the immune response induced by Th17 cells (Chu et al., 2016; Joller et al., 2014). When mice suffering from ulcerative colitis were orally infused with *Lactobacillus plantarum* and *Bifidobacterium,* the inflammatory response and the level of TNF-α were decreased, but the levels of superoxide dismutase 1 (SOD1) and SOD2 were increased (Wang et al., 2018). Dietary supplementation of *Bifidobacterium* can reduce the contents of LPS and proinflammatory factor to alleviate the intestinal inflammation (Yan et al., 2019). The SFB in the gut of mice can induce the expression of SAA. SAA in turn can induce the differentiation of Th17 cells in the lamina propria, increase the expression of IL-17 and IL-22, and lead to suppression of intestinal inflammation induced by the *Citrobacter rodentium* (Rong et al., 2006; Zheng et al., 2008).

Additionally, the pretreatment of bovine mammary epithelial cells (BMEC) with *Lactobacillus rhamnosus* can reduce the colonization of *E. coli* and can weaken inflammatory response and cellular damage by suppressing the activization of NLR family pyrin domain containing 3 (NLRP3) (Wu et al., 2016). Dendritic cells can decrease the number of TLR4 and the T cell quantity in the gut to limit the intestinal inflammation induced by bacteria (Ng et al., 2011). Toll-like receptor 4 pathway is an important inflammation signal pathway. Lipopolysaccharide combines with TLR4 through the delivery of CD14 and myeloid differentiated protein 2 (Tsukamoto et al., 2018). Then, TLR4 combines with MyD88 and activates IL-1 receptor related kinase, tumor necrosis factor receptor associated factor 6, NF-κB inhibitor kinase, and NF-κB to up-regulate the expression levels of *TNF-α*, *IL-6*, and *IL-1* (Yang et al., 2016). IL-6 is secreted by macrophages, T cells, B cells, and mesenchymal cells (Song et al., 2018). Before playing the biological role, IL-6 combines with IL-6 binding receptor protein and glycoproteins 30. IL-6 can increase the permeability of intestinal epithelial and can lead to the accumulation of T cells which maintain inflammatory response (Ma et al., 2018). Meanwhile, IL-6 can activate the classical complement pathway. It increases the number of complement 5a and the permeability of blood vessel, and then leads to tissue damage. TNF is divided into TNF-α, TNF-β, and TNF-γ. Especially, TNF-α can induce inflammatory response (Zhang et al., 2018). It is secreted by mononuclear macrophages, lymphocytes, and the inoblast (Chen et al., 2018). It can damage the integrity, increase the permeability of the intestinal barrier, and promote the secrete of proinflammatory cytokine to amplify the inflammatory response (Nguyen et al., 2018). TNF-α combines with TNF receptor 1, which is a membrane receptor, and leads to apoptosis by activating the TNF receptor 2 associated death domain protein, Fas-associated death domain protein (FADD), FADD like IL-1β converting enzyme, caspase-3, and caspase-9 (Song et al., 2019). Furthermore, intestinal flora can convert tryptophan to indole-3-formaldehyde which can alleviate the mouse dermatitis through suppressing the cytokine secretion of Th2 cells (Gostner et al., 2016). Short-chain fatty acids bind to the G protein coupled receptor 43 to reduce the inflammation of neutrophil granulocytes (Lim et al., 2015) and regulate inflammatory response by restraining the activation of NF-κB and the secretion of IL-12 and TNF-α (Lewis et al., 2010). *Lactobacillus* and *Bifidobacterium* can increase the number of Tregs to control the gut inflammation by limiting the activity of T cells and innate immune cells (Cebula et al., 2013). The high concentration of IgE in germ-free mice

can be decreased by commensal bacteria, which limits the inflammatory response induced by Th2 cells (Cahenzli et al., 2013).

6. Conclusions

Gut microbiome can influence the development of immune tissues, nonspecific immunity, specific immunity, and inflammation. *B. subtilis* and *B. fragilis* are proved to facilitate the development of immune tissues. *L. acidophilus, B. thetaiotaomicron*, and *F. prausnitzii* are important bacteria to regulate the nonspecific immunity by maintaining and strengthening the organizational barriers, increasing the number of innate immunocyte, and promoting the secrete of innate immune molecule. *Bifidobacterium, L. casei, Clostridium, B. subtilis, B. fragilis*, and SFB are believed to have closely related to specific immunity through MyD88, TGF-β, IL-1, IL-6, IL-17, IL-22, γ-PGA, and PSA. *B. fragilis, L. plantarum, Bifidobacterium*, and SFB can regulate the inflammation response by TLR, NF-κB, and MyD88. Although a considerable understanding now exists on the mechanism of gut microbiome–immune interaction, a significant gap still exists. A more systemic study is needed to explore the mechanism of molecular interactions between the immune system and the gut microbiome.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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