

REVIEW

The interplay between host immune cells and gut microbiota in chronic inflammatory diseases

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Many benefits provided by the gut microbiota to the host rely on its intricate interactions with host cells. Perturbations of the gut microbiota, termed gut dysbiosis, affect the interplay between the gut microbiota and host cells, resulting in dysregulation of inflammation that contributes to the pathogenesis of chronic inflammatory diseases, including inflammatory bowel disease, multiple sclerosis, allergic asthma and rheumatoid arthritis. In this review, we provide an overview of how gut bacteria modulates host metabolic and immune functions, summarize studies that examined the roles of gut dysbiosis in chronic inflammatory diseases, and finally discuss measures to correct gut dysbiosis as potential therapeutics for chronic inflammatory diseases.

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INTRODUCTION

The term ‘microbiota’ has been used to define the community of symbiotic microbes including bacteria, archaea, viruses, fungi and protozoa that have established their own niches within a host, and provide supporting roles in host immunity and metabolism.^{1,2} It was recently revised that a typical human adult harbors about 10^{13} – 10^{14} of bacteria, which is the same order as the number of total human somatic and germ cells.³ The intestinal tract is the largest reservoir of the microbiota in the human body.³ The intestinal microbiota typically consists of more than 1000 bacterial species whose composition remains relatively stable in each individual throughout adulthood but tremendously diverse between individuals.⁴ However, several catastrophic changes, such as use of antibiotics, infection, pregnancy and long-term changes of lifestyles, can alter the composition and diversity of the intestinal microbiota.⁵ Recently, interest in the role of gut microbiota in the human health and disease is being increased as new technologies for meta-analysis of microbial genomes and transcripts as well as metabolites produced by microbiota have become feasible at affordable cost.^{6,7} It is now widely recognized that the gut microbiota has essential roles in human metabolism, the development of the immune system, as well as resistance to colonization of enteric pathogens in the gut.¹

Given the diverse and critical roles of the gut microbiota in human health, perturbations in the microbial composition, termed dysbiosis, may have a profound negative impact on the

human immune system, contributing to various chronic inflammatory disorders. In this article, we review the role of the host–microbe interaction in the host immune system, discuss possible links between intestinal dysbiosis and chronic inflammatory diseases, and finally propose potential treatments for these diseases through correction of intestinal dysbiosis.

FUNCTION OF INTESTINAL MICROBIOTA IN THE HOST

The ‘external’ metabolic organ

The microbiota assists in the degradation of otherwise indigestible carbohydrates in the human intestine through some digestive enzymes derived from bacteria.⁸ Most nutrients produced by host enzymes are absorbed in the stomach and small intestine, whereas bacteria residing in the ileum usually utilize only simple carbohydrates as a major energy source.⁹ By contrast, the indigestible carbohydrates and proteins equivalent to 10–30% of the total ingested energy reach the colon,^{9,10} where these otherwise indigestible dietary carbohydrates and host-derived glycans are converted by enzymes produced by strict anaerobic bacteria to simple carbohydrates used as nutrients and energy (Figure 1).^{8,11} To do this, for instance, *Bacteroides* species possess a large number of genes that encode essential enzymes to degrade diverse complex carbohydrates, and members of the phyla Firmicutes, Actinobacteria and Verrucomicrobium produce nutritionally specialized enzymes that have a key role in the degradation of particular substrates, such as plant cell walls, starch particles and mucins.^{8,11}

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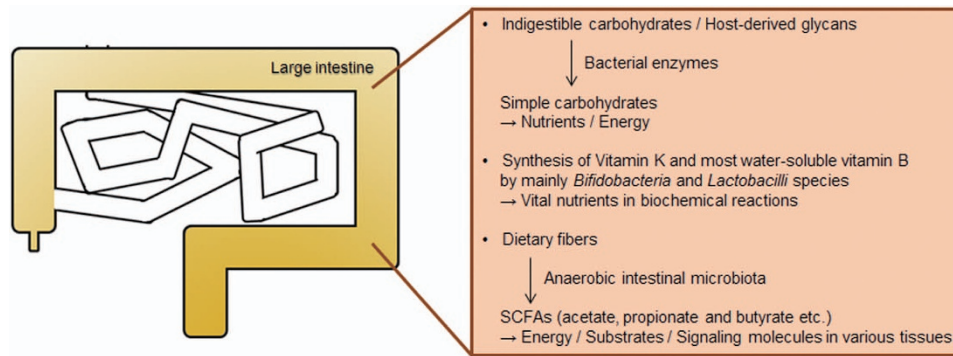


Figure 1 Functions of the microbiota in host metabolism. Some bacterial enzymes are capable of converting food- and host-derived carbohydrates to simple carbohydrates in the colon. Gut symbiotic bacteria such as *Bifidobacteria* and *Lactobacilli* are able to synthesize vitamin K and water-soluble vitamin B. SCFAs also are produced from diet fibers by Bacteroides, and used as nutrients, energy source and signaling molecules. SCFA, short-chain fatty acid.

Vitamins are vital nutrients that are necessary for essential biochemical reactions in living cells.¹² Intestinal bacteria act as an important supplier of vitamins along with foods.¹² *Bifidobacteria* and *Lactobacilli* species are recognized as beneficial probiotics capable of converting dietary compounds into vitamin K and most of the water-soluble vitamin B molecules including biotin, folates, nicotinic acid, pyridoxine, riboflavin, cobalamin and pantothenic acid (Figure 1).¹³ The vitamins synthesized by bacteria are mainly absorbed in the large intestine, whereas uptake of vitamins from dietary sources is achieved in the proximal small intestine.¹²

Also, anaerobic intestinal bacteria produce short-chain fatty acids (SCFAs) as the end products of fermentation of dietary fibers, among which, acetate, propionate and butyrate are the most abundant.^{14,15} SCFAs are transported from the intestinal lumen into the various tissues where they are used as either a source of energy, substrates or signal molecules, to aid in the metabolism of lipids, glucose and cholesterol (Figure 1).^{16–19} However, SCFA generation, diet and bacterial composition are delicately interlinked. For example, diets with high fiber-low fat and meat lead to higher amounts of SCFAs than diets with reduced fiber, thereby lowering the pH in the intestine and inhibiting the growth of pH-sensitive microbiota, which affects the production of SCFAs.^{20,21} Given the complexity of microbial metabolic pathways and cross-feeding mechanisms involved in SCFA production,¹⁵ there is not a simple linear correlation between intestinal SCFA levels and diet or microbial composition. Likewise, administration of a single dietary component or bacterial strain would unlikely result in an appreciable change in the concentration of SCFAs. Taken together, the intestinal microbiota essentially serves as ‘external metabolic organ’ that continuously supplies the host with absorbable nutrients and efficient energy.

Role of intestinal microbiota in the development and function of host immune system

Studies using germ-free (GF) and gnotobiotic animals, colonized with defined bacteria, have provided direct evidence that the microbiota has a crucial role in the development and

maintenance of the host immune system.^{2,22} Notably, GF mice show remarkable defects in the development of the gut-associated lymphoid tissues (GALT).^{2,22} For example, GF mice exhibit relatively fewer and smaller Peyer’s patches and mesenteric lymph nodes, and impaired development and maturation of isolated lymphoid follicles that serve as an inductive site for IgA responses, compared with the mice housed under specific pathogen free (SPF) conditions (Figure 2).^{22,23} However, the impaired development of these structures can be reversed by exposing GF mice to intestinal bacteria or peptidoglycans isolated from Gram-negative bacteria,^{22,23} showing that the microbiota has a dynamic relationship with the formation of GALT. The development and maturation of IgA-producing B cells are defective in the intestine of GF mice and sustained exposure to bacteria is required for the continued production of commensal-specific IgA.²⁴ In addition, the intestinal epithelial cells in GF animals are regenerated at a lower rate and form structurally altered microvilli compared with conventionally raised animals.²⁵ The intestinal mucus layer, which functions as a lubricant and protects the epithelium from irritations by luminal contents including certain microbes, is thinner in GF animals, indicating that resident bacteria are involved in the normal formation of the mucus layer.^{26,27} These defects in the intestinal physical barriers in GF animals seem to be associated with more susceptible phenotypes to pathogen infections and excessively heavy and prolonged bleeding during colitis induction.²⁸ Moreover, typical properties of mucus layer could be changed by certain bacteria and their community. For example, an increase in the abundance of Proteobacteria and TM7 bacteria in the gut drastically enhanced the permeability of the normally sterile mucus inner layer to more penetrable region, resulting in bacterial infiltration into intestinal inner layer close to epithelium.²⁷

Symbiotic intestinal bacteria have been well known to be essential for the development and function of specific lymphocyte subsets. GF mice and antibiotic-treated mice show reduced numbers of mucosal T helper (T_H)17 cells and type 3 innate lymphoid cells (Figure 2), which are involved in the resistance

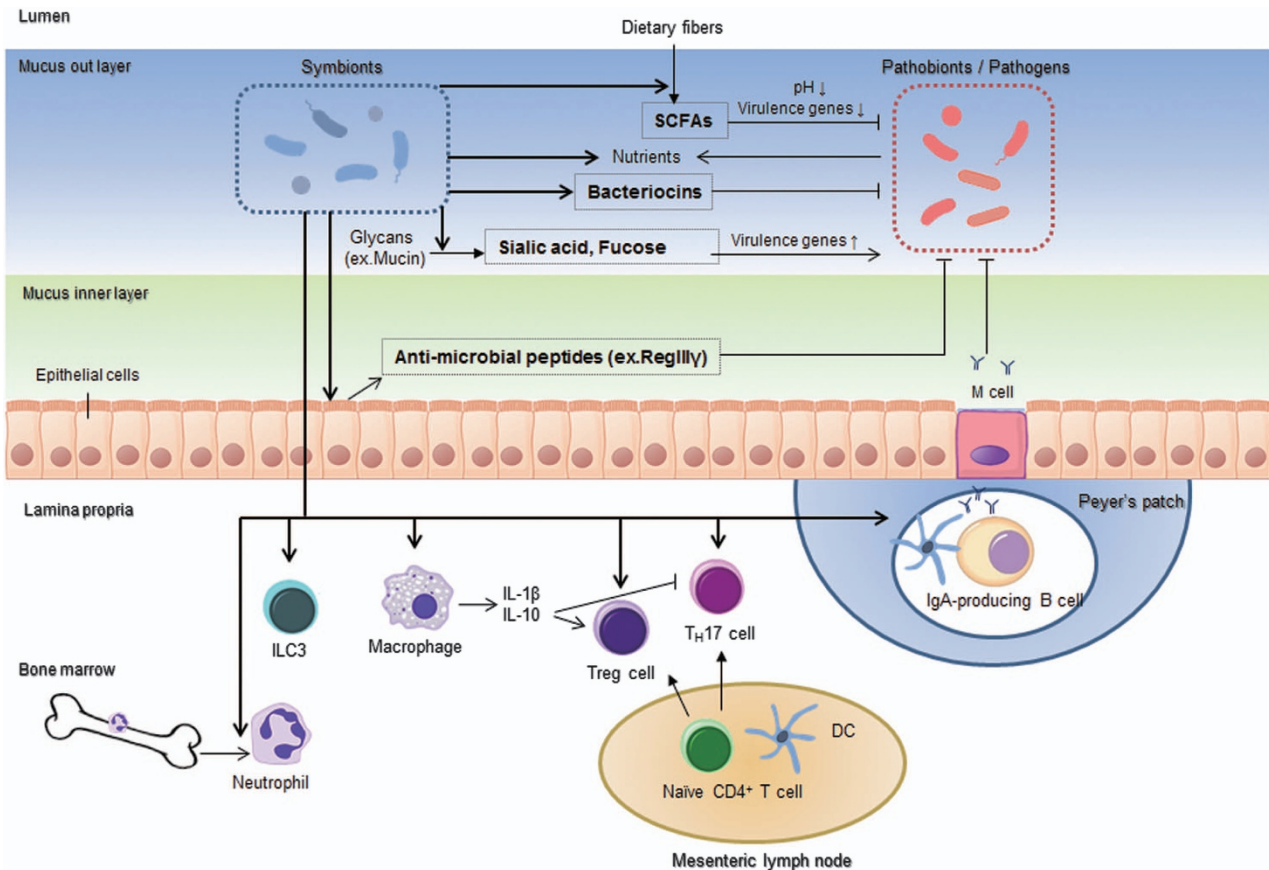


Figure 2 Symbionts directly and indirectly regulate the growth and colonization of pathobionts and pathogens. Symbionts outcompete pathobionts and pathogens by consuming limited nutrients, producing bacteriocins and lowering luminal pH through SCFA production. SCFAs and byproducts produced by symbionts regulate the expression of virulence genes in the pathobionts and pathogens. Moreover, symbionts elicit the host immune responses, such as recruitment of neutrophils, cytokine production of macrophages, differentiation of T_H17 , ILC3 and Treg cells, IgA production by B cells, and antimicrobial peptides production from epithelial cells. SCFA, short-chain fatty acid.

to extracellular microbes and the pathogenesis of autoimmune diseases by secreting interleukin (IL)-17 and IL-22.^{4,29} Moreover, mice lacking segmented filamentous bacteria (SFB) in their gut microbiota have fewer T_H17 cells in the small intestine than in mice with abundant SFB.²⁹ Normal developments of mucosal T_H17 cells can be restored following reconstitution with conventional microbiota or SFB alone (Figure 2).²⁹ However, SFB are not the only bacteria that possess T_H17 -inducing capacities. GF mice colonized with Altered Schaedler Flora (ASF), a cocktail of 8 defined commensals including *Clostridia*, also showed significantly increased numbers of T_H17 cells, albeit to a lesser extent as observed in SFB-colonized GF mice.³⁰ Likewise, the number of regulatory T cells (Tregs), which suppress immunopathology mediated by effector T cells and induce tolerance toward self-components, is reduced in the intestinal lamina propria of both GF and antibiotic-treated mice, whereas recolonization with conventional microbiota or selective species of bacteria restore the Treg cell population (Figure 2).⁴ For example, the administration with *Bacteroides fragilis* or its product, polysaccharide A, induces the development of Tregs and production of IL-10, anti-inflammatory cytokine in the intestine.³¹

Furthermore, Kenya Honda and colleagues have reported unique Treg-inducing activities in indigenous *Clostridia* species isolated from mice and healthy humans (Figure 2).³²

Important roles for the gut microbiota in innate immunity in the gut have been documented as well. Phagocytes, such as macrophages and neutrophils, are tightly regulated to maintain intestinal homeostasis.⁴ Intestinal bacteria continuously stimulate resident macrophages to release large amounts of IL-10 that promotes induction of Treg cells and prevents excessive development of T_H17 cells, which is critical for maintaining tolerogenic immune responses in the intestine (Figure 2).³³ The stimulation by commensals also upregulates the expression of pro-IL-1 β (precursor form of IL-1 β) in intestinal phagocytes without eliciting inflammasome responses and harmful release of mature IL-1 β .³⁴ During infection of pathogens, such as *Salmonella* and *Pseudomonas aeruginosa*, however, maturation and secretion of IL-1 β immediately occurs by the activation of inflammasome through Nod-like receptors, NLRC4, that are expressed in intestinal phagocytes to protect the host from pathogens.³⁴ The numbers of circulating and bone marrow neutrophils are also affected by the microbiota as well.³⁵ For example, intestinal microbiota augments host response against

pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, through constitutive stimulation of neutrophils derived from the bone marrow (Figure 2).³⁶

Direct and indirect regulation of pathogens by commensals

Some of commensals beneficial to the host are referred to as symbionts, whereas others that post harmful effect to the host under certain situations are called pathobionts.^{2,37} The commensal microbiota regulates the colonization of pathobionts

and invading pathogens in both a direct and indirect manner. Symbionts produce bacteriocins, proteinaceous toxins, that most directly target and kill similar or closely related bacterial strains (Figure 2).³⁸ Also, symbionts and metabolically related pathobionts or pathogens compete for limited nutrients, which gives symbionts the unique ability to resist colonization of related pathobionts or pathogens in the gut (Figure 2). For example, *Citrobacter rodentium*, an enterohaemorrhagic *Escherichia coli* (EHEC) mouse strain, could be outcompeted by

Table 1 Studies investigating intestinal microbiota in patients

Disease subjects	Methodology	Alteration in microbiota	References
<i>Intestinal bowel disease</i>			
UC patients	Terminal restriction fragment length polymorphism	Diversity of mucosa-associated microbiota ↓	49
CD patients	16S rRNA gene sequencing/fluorescent <i>in situ</i> hybridization	Diversity of phylum <i>Firmicutes</i> ↓	48
CD patients	16S rRNA gene sequencing	<i>Faecalibacterium</i> and <i>Roseburia</i> ↓ <i>Enterobacteriaceae</i> and <i>Ruminococcus gnavus</i> ↑	52
CD patients	16S rRNA gene sequencing/fluorescent <i>in situ</i> hybridization	<i>Faecalibacterium prausnitzii</i> , <i>Ruminococcus bromii</i> , <i>Oscillibacter valericigenes</i> , <i>Bifidobacterium bifidum</i> , and <i>Eubacterium rectale</i> ↓ <i>Escherichia coli</i> , <i>Enterococcus faecium</i> and species from the Proteobacteria ↑	51
UC and CD patients	16S rRNA gene sequencing	Members of the phyla <i>Firmicutes</i> and <i>Bacteroidetes</i> ↓	50
<i>Multiple sclerosis</i>			
MS patients	Fluorescent <i>in situ</i> hybridization	<i>Faecalibacterium</i> ↓	71
MS patients	16S rRNA gene sequencing	<i>Faecalibacterium</i> , <i>Prevotella</i> , and <i>Anaerostipes</i> ↓	72
Relapsing-remitting MS patients	16S rRNA gene sequencing	<i>Parabacteroides</i> , <i>Adlercreutzia</i> and <i>Prevotella</i> ↓ <i>Psuedomonas</i> , <i>Mycoplana</i> , <i>Haemophilus</i> , <i>Blautia</i> , and <i>Dorea</i> ↑	73
<i>Allergic diseases</i>			
Atopic patients (newborn ~2 years old)	Bacterial cultivation	<i>Bacteroides</i> , <i>Bifidobacteria</i> ↓ <i>Enterococci</i> , <i>Clostridia</i> , <i>Staphylococcus aureus</i> ↑	83
Atopic patients (2 years old)	Quantitative real-time PCR	<i>E. coli</i> and <i>Clostridium difficile</i> ↑	84
Atopic patients (3 weeks ~3 months old)	Bacterial cultivation/ gas-liquid chromatography/fluorescence <i>in situ</i> hybridization	<i>Bifidobacteria</i> ↓ <i>Clostridia</i> ↑	85
Asthma patient (school age)	16S rRNA gene sequencing /barcoded 16S rDNA 454 pyrosequencing	Diversity of total microbiota ↓	91
<i>Rheumatoid arthritis</i>			
RA patients	Metagenomic sequencing and assembly	<i>Haemophilus</i> spp. ↓ <i>Lactobacillus salivarius</i> ↑	96
RA patients (new-onset)	16S rRNA gene sequencing	<i>Prevotella</i> (<i>P. copri</i>) ↑	97
RA patients (early)	Quantitative real-time PCR	<i>Lactobacillus</i> ↑	99
RA patients	16S rRNA gene sequencing	<i>Faecalibacterium</i> ↓ <i>Eggerthella</i> and <i>Collinsella</i> ↑	100

Abbreviations: CD, Crohn's disease; MS, multiple sclerosis; RA, rheumatoid arthritis; UC, ulcerative colitis.
↓ Decreased, ↑ increased, when compared with the healthy subjects.

commensal *E. coli* strains, but not commensal *Bacteroides*, through competitions for simple sugars.³⁹

Certain commensal bacteria can indirectly regulate the colonization of pathogens through their byproducts (Figure 2). *Bacteroides thetaioaomicron* has sialidase and fucosidase activities, which mediate the production of sialic acid and fucose from host mucus, respectively.⁴⁰ Sialic acid can be catabolized by both *Salmonella enterica* serovar Typhimurium and *Clostridium difficile*, to promote the growth of these two pathogens.⁴¹ Fucose induces the expression of virulence genes in EHEC through the fucose receptor signaling cascade, which in turn facilitate vigorous colonization of EHEC.⁴² The intestinal microbiota also produces several SCFAs as the end products of fermentation of dietary fibers.^{14,15} The low pH from the ileum to the cecum is attributed to high concentrations of SCFAs, which inhibits the growth of pH-sensitive pathogenic bacteria, such as *E. coli* pathogenic strain and *Salmonella* (Figure 2).^{20,21} Moreover, SCFAs regulate the expression of virulence gene in some pathogens, such as *Salmonella*, *E. coli*, *Campylobacter jejuni*, and *Campylobacter jejuni*.⁴³

In addition, the microbiota indirectly exerts protective effects on pathogens by stimulating the host immune system. The epithelium stimulated by the microbiota produces mucus and antimicrobial peptides, which are critical to the maintenance of a sterile mucus inner layer against both commensals and pathogens (Figure 2).²⁷ Although several antimicrobial proteins, such as α -defensins, are constitutively expressed without bacterial signals, Gram-negative bacteria, like *B. thetaioaomicron*, but not Gram-positive microbes, induce the expression of RegIII γ , a key subset of antimicrobial peptides, which has a specific microbicidal effect on Gram-positive bacteria.^{44,45} Direct and indirect regulation of pathogens by commensals prevents the attachment of pathogens to the surface of intestinal epithelium at initial stage of enteric infection.

ROLE OF INTESTINAL MICROBIOTA IN CHRONIC INFLAMMATORY DISEASES

Inflammatory bowel disease

Inflammatory bowel disease (IBD), in the form of ulcerative colitis (UC) or Crohn's disease (CD), is a chronic inflammatory disease caused by a combination of genetic, environmental and microbial factors.⁴⁶ The first evidence that intestinal bacteria are involved in the pathogenesis of IBD came from a clinical study showing that fecal stream diversion can improve the symptoms of CD.⁴⁷ Since then, many studies have supported that IBD is directly and indirectly associated with alterations of the intestinal microbiota. Several metagenomic analyses revealed the reduced diversity of fecal microbiota in patients with colitis compared with that in healthy controls (Table 1).^{48,49} In addition, patients with CD or UC have reduced numbers of members of the phyla Bacteroidetes and Firmicutes, whereas species belonging to the phyla Actinobacteria and Proteobacteria, such as *E. coli*, are increased in mucosa-associated microbiota (Table 1).^{6,50–52} It has been

speculated that intestinal dysbiosis might not be a mere consequence but rather a cause of IBD pathogenesis. For instance, more bacteria penetrate the intestinal mucus layer in patients with IBD than that observed in healthy controls, indicating possibly more virulent intestinal bacteria in patients with IBD that possess a heightened accessibility to the epithelial mucus layer.⁵³ Consistently, increase in the relative proportion of *Bacteroidales* and *Clostridiales* is likely to trigger inflammation in high-fat-fed rat models.⁵⁴ However, many bacterial species, such as *Enterobacteriaceae*, appear to have the unique ability to bloom in an inflammatory environment,⁵⁵ suggesting that it is likely that many or most of the changes in microbiota composition observed in IBD are secondary to inflammation rather than the cause of colitis.

Preclinical studies in animals provide evidence to support that altered microbial composition of the gastrointestinal tract contributes to the development of IBD. Animals with spontaneous or DSS-induced colitis develop only minor inflammation under GF conditions.^{56–58} Moreover, a number of studies have shown that certain pathobionts can contribute to the induction of colitis in genetically IBD-prone animals, and other bacteria have an opposing role. For example, *E. coli* or *Enterococcus faecalis* promote the occurrence of colitis in *Il-10*- or *Il2*-deficient mice, which could be reversed by colonization with *Bacteroides vulgatus*.^{59–61} In addition, the reduction of *Bacteroides fragilis* and *Faecalibacterium prausnitzii*, which correlates with higher risks for CD in humans, might promote intestinal inflammation through downregulation of Treg cells.^{62–64} In addition, Enterobacteriaceae species *Klebsiella pneumoniae* and *Proteus mirabilis* were shown to correlate with spontaneous development of colitis in *T-bet*^{-/-} \times *Rag2*^{-/-} mice, perhaps in part because of their abilities to potently induce TNF α in innate immune cells.⁶⁵ These observations demonstrate immunomodulatory effects of gut symbiotic bacteria in the pathogenesis of IBD, and also shed light on potential therapeutic approaches directed at specific pathobionts for the treatment of IBD.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disorder of the central nervous system (CNS) that causes neurological dysfunctions such as blindness, paresis and sensory disturbances.⁶⁶ The importance of intestinal microbiota in the occurrence of MS was first suggested by several preclinical studies using an experimental autoimmune encephalomyelitis (EAE) model, a murine model of MS.⁶⁶ GF mice fail to develop spontaneous and inducible EAE, which is attributed to impaired generation of T_H17 cells.^{67,68} Likewise, antibiotic treatments that induced Treg cells and IL-10-producing B cells were shown to suppress clinical severity in EAE model.⁶⁹ Moreover, mono-colonization with SFB, known to induce the T_H17 population in the intestine, can induce EAE in the GF mice, whereas colonization of *B. fragilis* or administration of *B. fragilis*-derived polysaccharide A, maintains the resistance to EAE through induction of Treg cells.^{68,70} These results indicate potential roles for certain gut

symbiotic bacteria in the pathogenesis of the EAE model through their abilities to modulate immune responses.

Up to date, few but highly informative metagenomics studies have been performed to investigate a clinical correlation between gut microbiota and MS. Patients with MS have significantly altered microbial profiles in the intestine compared with the healthy people, in spite of insignificant differences in bacterial richness and diversity between these two groups. For instance, individuals with MS have less *Faecalibacterium* that produce the anti-inflammatory SCFA butyrate (Table 1),⁷¹ as well as decreased levels of the bacterial genus *Prevotella* (Bacteroidetes phylum) and the genera *Faecalibacterium* and *Anaerostipes* (both of Firmicutes phylum) (Table 1).⁷² A very recent study reported reduced abundance in the genera *Parabacteroides*, *Prevotella* (both of Bacteroidetes phylum) and *Adlercreutzia* (Actinobacteria phylum) in the feces from patients with relapsing-remitting MS, whereas the general *Pseudomonas*, *Mycoplasma*, *Haemophilus* (above Proteobacteria phylum), *Blautia* and *Dorea* were more abundant in these patients (Table 1).⁷³ Thus far, studies have suggested intestinal dysbiosis characterized by overall decreases in Bacteroidetes and Firmicutes phyla correlates with the development of MS. However, additional studies are required to delineate the mechanisms underlying intestinal dysbiosis-mediated immune dysregulation that is associated with the development of MS.

Asthma and allergic diseases

Allergic asthma is a chronic inflammatory disorder associated with T_H2-driven inflammatory responses to inhaled innocuous allergens, resulting in airway hyper-responsiveness and tissue remodeling of airway structures, and bronchial obstruction.^{74,75} About 300 million people worldwide are affected by allergic asthma, characterized by recurrent episodes of wheezing as a result of mucus plugging, bronchial mucosal thickening and bronchoconstriction.⁷⁵ The diversity of microbial stimuli exposed to during early childhood, such as breastfeeding, having multiple siblings, contacting farm animals and pets, leads to protective mechanisms against asthma.^{76–79} One theory is that microbial products trigger innate immune response through pattern-recognition receptors, such as the Toll-like receptors, which may activate several signaling pathways such as induction of Treg cells, as well as Type 1 helper T (Th1) cells, which can counter-balance the predominance of Th2 cells that mediate asthmatic attacks. In support of this theory, GF mice that have been sensitized and challenged with ovalbumin (OVA) suffer from more exaggerated allergic airway inflammation than SPF mice,⁸⁰ indicating the importance of microbiota in the prevention of asthma development. Intriguingly, this severe inflammation could be restored by colonization with a conventional microbiota in neonatal GF mice, but not in adult GF mice.⁸¹ In support of this hypothesis, Olszak *et al.*⁸¹ revealed that microbial colonization in neonatal mice can contribute to the reduced expression of *Cxcl16* mRNA in the colon, ileum and lung by inhibiting hypermethylation of *Cxcl16*, thereby reducing the recruitment of iNKT cells into these tissues, which alleviates allergic airway inflammation in

response to OVA. This observation also implicates that epigenetic modifications of *Cxcl16* gene seen during childhood by diverse microbial exposure cannot be achieved later in adulthood even with the same microbial exposure.⁸¹

In addition to the exposure to microbes early in life, the microbial composition is also an important factor to dictate development of the allergic diseases. Several studies have reported distinct patterns in the intestinal microbiota infants that developed allergies later in life.^{82–85} The intestinal flora of babies that suffered from allergic inflammation, consists of more prevalent *Clostridia* and *Enterococci* and less prevalent *Lactobacilli*, *Bifidobacteria* and Bacteroidetes compared with healthy subjects (Table 1).^{83–85} The childbirth process has a significant impact on the formation of microbial community in neonates. Infants delivered through vaginal tract typically form a microbial composition including abundances of *Snethia* and *Lactobacillus* spp., which is substantially similar to that found in the mother's vaginal tract; whereas infants born via cesarean section possess a microbiota enriched with *Staphylococcus* and *Streptococcus* spp., similar to that of maternal skin microbiota.⁸⁶ The latter has been reported at significantly higher risks for allergic diseases.⁸⁷ Also, use of antibiotics by the mother during pregnancy or the infant affects the microbial communities in the lung and intestine of the infant, which is associated with increased incidence of asthma and other allergic diseases later in life.^{88,89}

Microbes residing in the respiratory tract are naturally associated with asthma development.⁹⁰ Surprisingly, intestinal microbiota appears to contribute to allergic airway inflammation. For instance, children developing asthma have a lower diversity in intestinal microbiota than non-asthmatic children do (Table 1).⁹¹ Oral administration with *Lactobacillus reuteri* leads to an increase in Treg cell population in the blood, spleen and mediastinal lymph nodes, resulting in reduction of asthmatic responses in mice with OVA sensitization and challenge.⁹² Similarly, mice treated with a cocktail of *Clostridium* strains have reduced IgE production after OVA sensitization, likely because of the induction of Treg cells in the colonic mucosa by these *Clostridium* strains.³² Moreover, a high-fiber diet increases the ratio of Firmicutes to Bacteroidetes in the intestine, which elevates the levels of circulating SCFA, is associated with protection against airway inflammation.⁹³ These observations suggest that intestinal microbiota, through yet undefined mechanisms, may polarize immune cells such as T helper cells that either promote or favor the development of allergic inflammation.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that symmetrically affects large and small joints with inflammation and ultimately incurs in joint deformity.⁹⁴ The relatively higher concordance of 12–15% in monozygotic twins than 2–4% in dizygotic twins suggests the contribution of genetic factors to RA pathogenesis.⁹⁵ However, the low concordance even in monozygotic twins indicates the importance of environmental factors as well.⁹⁵ In addition to

genetic and environmental factors, a number of studies have provided evidence that microbial factors are involved in the development of RA. A metagenomic analysis of fecal, dental and salivary samples showed that the microbial community of RA patients can be distinguished from that of healthy subjects.⁹⁶ For instance, individuals with RA have relatively high abundance of *Lactobacillus salivarius* in their intestine and oral cavity, which correlates with clinical severity.⁹⁶ In addition, the number of *Prevotella copri* is increased in patients in the first year after RA onset (Table 1).⁹⁷ Similarly, other studies also showed a positive correlation between *P. copri* and early development of RA in untreated patients^{97,98} and increased amounts of *Lactobacillus* species in early RA patients (Table 1),⁹⁹ although it remains unclear how/whether higher abundance of these bacterial species have a role in the development of RA. Moreover, patients with RA exhibit reduced microbial diversity in their intestines compared with controls, which is proportional to increased disease duration and autoantibody levels.¹⁰⁰ The dysbiosis in RA individuals is characterized by an increase of harmful microbes including *Eggerthella* and *Collinsella* and a decrease of beneficial bacteria such as *Faecalibacterium*, one of the most abundant Firmicutes in the human gut (Table 1).¹⁰⁰ Interestingly, treatment with disease modifying anti-rheumatic drugs (DMARDs) can reverse this perturbation of intestinal flora in RA patients closely to that of healthy individuals.⁹⁶ Hence, the microbial profile in the intestine might be used as a marker of RA development.

Spontaneous arthritis models, such as SKG, K/BxN and IL-1 receptor antagonist knockout (*Il1ra*^{-/-}) mice and HLA-B27 transgenic rats, fail to induce arthritis under GF conditions.^{56,101–103} In contrast, F344 rats develop severe arthritis induced by adjuvant stimulation when raised under GF conditions.¹⁰⁴ Despite these conflicting results, the microbiota may modulate the sensitivity of arthritis models possibly through modulation of the immune response. Furthermore, *Collinsella* and *P. copri* that are abundant in RA patients, aggravate disease severity in a humanized arthritis model and the SKG model, respectively,^{98,100} suggesting that these two bacteria might indeed have a role in the pathogenesis of RA. However, more work is needed to understand the role of the microbiota in RA development.

MICROBIOTA-TARGET TREATMENT

As described so far, intestinal dysbiosis observed in various chronic inflammatory disorders, such as IBD, MS, allergic asthma and RA, has been suggested to contribute to the pathogenesis of these diseases. Thus, approaches to remove disease-causing pathobionts or boost beneficial symbionts now emerge as promising therapeutics to mitigate dysregulated inflammation underlying these diseases.

Antibiotics

Antibiotic treatment used in the clinical setting has been mainly used to either treat or prevent infection.^{105,106} However, simultaneously, it can cause unintended damage by depleting beneficial commensals^{105,106}

Even though the microbiota can be restored to the original status following withdrawal of antibiotics, in some cases, full restoration may not be achieved after prolonged treatment.¹⁰⁶ In some other cases, blooms of pathobionts, albeit temporary, may pose long-lasting negative impacts on host immune responses or other functions.¹⁰⁷ It should be noted that the scale and persistence of such perturbations depends on the class of antibiotics administered. For example, the administration of either a combination of amoxicillin, metronidazole and bismuth, or vancomycin alone, significantly reduces microbial diversity in intestinal microbiota; whereas compositional alterations can be almost fully reversed to baseline about 3 weeks after termination of antibiotic treatment.¹⁰⁵ In contrast, following administration with clindamycin, which has a strong and broad activity against almost anaerobes, for 7 days, the diversity of *Bacteroides* is never restored to its original level until over two years of recovery.¹⁰⁷ Antibiotic-induced alterations of the gut microbiota can promote various diseases. For instance, antibiotic treatments lead to an increase in the abundance of host-derived free sialic acid in the intestine, which can then be utilized by certain pathogens and pathobionts, such as *S. enterica* serovar Typhimurium and *C. difficile*, resulting in blooms of pathogenic bacteria in the intestinal tract and subsequently symptoms including diarrhea.⁴¹

Therefore, the use of narrow-spectrum antibiotics appears as an appealing alternative to minimize the risk of gut dysbiosis and blooms of pathobionts.¹⁰⁸ There has been an increasing interest in the use of ampicillin and penicillin, relatively narrow-spectrum antibiotics, for the management of hospitalized infants and children with community-acquired pneumonia.¹⁰⁹ A follow-up study of this strategy showed that ampicillin and penicillin have a similar efficacy with empirically used broad-spectrum antibiotics.¹¹⁰ Like this, it remains challenging to determine which narrow-spectrum antibiotics have sufficient efficacy and specificities against particular infectious agents to replace the empirically used broad-spectrum antibiotics. To do that, understanding the mechanisms by which pathogens colonize the intestinal tract, outcompete commensal bacteria, or translocate systemically as well as finding intrinsic factors that can differentiate pathogens from commensals, will provide critical insights into the development of effective and specific narrow-spectrum antibiotics that target the pathogens or selective pathobionts, whereas remaining innocuous to other commensals.

Probiotics

Probiotics are live microorganisms that provide health benefits to the host when consumed in adequate amounts.¹¹¹ For many years, studies of probiotics have reported prophylactic and therapeutic effects of probiotics in the various disease models associated with intestinal dysbiosis. For instance, a probiotic cocktail composed of four *Lactobacillus* and *Bifidobacterium* strains attenuates severity of acute colitis.¹¹² A mixture of five probiotics, consisting of *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum* and

Streptococcus thermophiles, has prophylactic and therapeutic effects in the murine EAE model through decreases in T_H1 and T_H17 cells and induction of Treg cells.¹¹³ Oral administrations of *Lactobacillus rhamnosus* attenuates OVA-induced airway inflammation.¹¹⁴ Also, *L. casei* and *L. acidophilus* diminish arthritic symptoms in the collagen-induced arthritis model by inhibiting proinflammatory cytokines and inducing anti-inflammatory cytokines.¹¹⁵

Compared to preclinical data, available clinical reports on the benefits of probiotics, however, are scarce.¹⁰⁸ A randomized trial showed that consumption of a probiotic drink containing *Lactobacillus casei*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* reduced the risk of antibiotic-associated diarrhea and *Clostridium difficile* infection (CDI) in a small number of patients over the age of 50.¹¹⁶ A meta-analysis of sixteen randomized, parallel, controlled studies (3432 participants) of the incidence of antibiotic-associated diarrhea in children treated with adjunctive probiotic therapy supported that potential of probiotics to prevent antibiotic-associated diarrhea.¹¹⁷ In addition, a probiotic combination of *Lactobacillus acidophilus* and *Bifidobacterium lactis* was shown to reduce birch pollen allergy symptoms including infiltration of eosinophils.¹¹⁸ Despite results from these clinical studies, the administration of probiotics is not strongly recommended, due to insufficient data to support their preventive or therapeutic efficacy and conflicting reports on their benefits.¹⁰⁸ Alternatively, consumption of prebiotics, which are mostly plant-derived fibers that selectively enrich beneficial bacteria, may have advantages over probiotic therapy to introduce more persistent and stable compositional changes to a dysbiotic microbial community. Further investigations of the mechanisms of protection by probiotics or prebiotics will advance the design of probiotics-based therapeutics to correct dysbiotic microbiota that could potentially promote development of disease if untreated.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) refers to the transfer of the entire fecal microbial community from a healthy donor into a recipient patient with the goal to completely restore healthy microbial community in the patient.¹¹⁸ FMT has been used for patient with recurrent CDI.¹¹⁹ As predicted, CDI patients treated with FMT exhibited the microbial structural changes more similar to the donor profile than bacterial flora prior to transplant, which resulted in functional changes and hence therapeutic effects.¹²⁰ Promising results were observed in using FMT to treat IBD as well. A meta-analysis of previous nine case studies of IBD patients treated with FMT showed that a pooled proportion achieving remission was 22% in UC patients and 60.5% in CD patients.¹²¹ Given that the microbial basis of IBD is far more complex and variable than that of recurrent CDI, the results suggest a positive effect of FMT, albeit at a lower successful rate compared with that achieved by FMT in recurrent CDI (between 80 and 95% efficacy).¹¹⁹ Overall, the efficacy of FMT in IBD treatment needs to be corroborated by additional large-scale clinical studies.

The potentials of FMT to improve other chronic inflammatory diseases associated with intestinal dysbiosis, however, have not been extensively explored. Recent studies have begun to investigate the effect of FMT on MS patient treated with FMT.¹²² Therefore, further studies are required to determine the roles of FMT in the treatment of other inflammatory disorders including MS.

CONCLUSION

Knowledge related to the interplay between the microbiota and the human immune system is being accumulated at a remarkable rate, as metagenomic and metatranscriptomic approaches to the microbiome and metabolomic analysis of small metabolites at affordable cost have been possible.¹²³ The information reveals us that the microbiota is no longer a by-stander in human health, disease and survival. As described in this review article, the intestinal microbiota is likely to be involved in the pathogenesis of various chronic inflammatory diseases, such as IBD, MS, allergic asthma and RA. Particular bacterial species with the gut microbial community have been identified to directly or indirectly contribute the onset and deterioration of these disorders. Therefore, measures to correct intestinal dysbiosis, such as FMT may offer long-lasting and effective ways to mitigate dysbiosis-induced inflammation that in part promotes the manifestation of the aforementioned diseases. Further identification of the specific symbiotic bacteria capable of inhibiting the colonization of pathogenic bacteria and promoting host immunity and metabolism will aid in developing microbiota-based precision medicine to reverse dysbiosis-induced and disease-associated defects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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