CURRENT OPINION

Gut microbiome and its clinical implications: exploring the key players in human health

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Purpose of review

The human gut harbors a diverse community of microorganisms known as the gut microbiota. Extensive research in recent years has shed light on the profound influence of the gut microbiome on human health and disease. This review aims to explore the role of the gut microbiome in various clinical conditions and highlight the emerging therapeutic potential of targeting the gut microbiota for disease management.

Recent findings

Knowledge of the influence of gut microbiota on human physiology led to the development of various therapeutic possibilities such as fecal microbiota transplant (FMT), phage therapy, prebiotics, and probiotics. Recently, the U.S. FDA approved two FMT products for the treatment of recurrent *Clostridioides difficile* infection with ongoing research for the treatment of various disease conditions.

Summary

Advancement in the knowledge of the association between gut microbiota and various disease processes has paved the way for novel therapeutics.

Keywords

dysbiosis, fecal microbiota transplant, gut microbiome, gut microbiota, mucosal immunity

INTRODUCTION

The gut microbiota consists of trillions of microorganisms such as bacteria, viruses, fungi, phages, archaea, and other microbial species that reside in the gastrointestinal tract. Gut microbiota consists of six major phyla such as Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. The most commonly found fungi in gut microbiota are Candida, Saccharomyces, Malassezia, and Cladosporium [1▪,2]. Microbiome refers to the collection of genomic material from all microorganisms in an environment [3]. Recent advances in next-generation sequencing (NGS) technology have enabled us to gain an in-depth understanding of the intricate relationship between the human gut microbiome and the diseases associated with them. 16S rRNA advanced sequencing data showed that *Firmicutes* and *Bacteroidetes* make up approximately 92% of the human gut microbiome [4]. The components of the gut microbiome vary significantly between individuals and correlate with environmental changes and genetic inheritance [5,6].

The symbiotic relationship between the microbiome and the gut environment has been maintained throughout evolution. The gut provides nutrients and a fertile environment for the gut microflora, which in turn aids in the fermentation of carbohydrates and the synthesis of vitamins. The gut microbiota is closely linked to the intestinal mucosal immune system, the largest immune system in vertebrates [5]. In this review, we will primarily focus on the role of the gut microbiome in the homeostasis of the mucosal immune system and the effect of dysbiotic microbiota in human disease.

GUT MICROBIOME AND INTESTINAL MUCOSAL IMMUNE SYSTEM

Gastrointestinal tract plays a critical role in the digestion of food, the uptake of nutrients, and the

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KEY POINTS

- Gut microbiome plays a crucial role in maintaining homeostasis of the gut mucosal immunity.
- Significant risk factors contributing to gut dysbiosis include diet, lifestyle, and antibiotic use.
- Gut microbiota dysbiosis is associated with various disease processes.
- Fecal microbiota transplant (FMT) is novel and FDA-approved for the treatment of recurrent *Clostridioides difficile* infection and is under research for the management of other diseases.

elimination of toxic waste. In these processes, the mucosa covering the gastrointestinal tract is continually and directly exposed to a wide range of microbes and food antigens [7]. Furthermore, the intestine is a primary route of entry for a variety of bacteria and viruses, and has a high level of colonization, culminating in a combination of various microbial communities [8]. The mucosal immune system is the largest part of the body, making up about 75% of the total number of lymphocytes and creating most of the immunoglobulins in healthy people. In contrast to systemic immunity, mucosal immunity must strike a balance between the requirement to protect against pathogens and the need to avoid overreacting to the commensal gut flora. Innate functional immune cells, such as granulocytes, macrophages, and dendritic cells express invariant receptors to detect microbes. Adaptive immune cells such as B and T cells express more variable receptors that recognize specific antigens [7].

Immune cells are found in the gut in the arrangement of secondary lymphoid structures called gut-associated lymphoid tissue (GALT), and mesenteric lymph nodes reside between epithelial cells and connective tissue. The mucus layer on the intestinal epithelial cell surface is the first layer of protection in the gut mucosal immune system [9]. The epithelial layer consists of intestinal stem cells, which are found in the crypts at the base. Intestinal goblet cells form a mucous layer that reduces the intestinal epithelial cell's exposure to microorganisms. In addition, Paneth cells secrete antimicrobial peptides (AMPs) including Alpha-Defensins (ADP), lysozyme, and secretory phospholipase A2 into the mucus layer, which helps in preventing antigen exposure to intestinal epithelial cell surface [10]. Plasma cells secrete IgA, which binds to the mucus and prevents pathogenic organisms from entering, and helps maintain homeostasis among the host gut microbiota [11]. Epithelial cells and innate immune cells detect microbiota through recognition receptors, including toll-like receptors (TLRs). Macrophages are located beneath the epithelial cells and are responsible for the phagocytosis of invading microorganisms, as well as disposing of pathogens that are targeted by adaptive immune cells. Innate lymphoid cells (ILCs), on the contrary, are responsible for regulating tissue homeostasis, repair and remodeling, as well as microbial defense. Dendritic cells detect antigens either by sampling luminal antigens via the membranous process inserted between the intestinal tight junction or via microfold cells. Following the acquisition of antigens by dendritic cells, they remain in Peyer's patches or migrate to the mesenteric lymph node to interact with naive T cells. Retinoic acid and transforming growth factor β (TGF-β) is produced by dendritic cells to stimulate the production of regulatory T-lymphocytes (Tregs), which in turn secrete higher amount of anti-inflammatory interleukin-10 (IL-10) and TGF-β. When naive B cells come into contact with antigens in Peyer's patches and mesenteric lymph nodes, they differentiate into antibody-secreting plasma cells or memory B cells. These plasma cells may be short-lived or long-lived and can undergo isotype switching from IgM to IgA. IgA carries antigens across epithelium to neutralize toxins and pathogens, without causing inflammation (illustration in Fig. 1) [12].

The gut microbiome plays a critical role in the development of intestinal mucosal immunity, which is essential for the homeostasis and defense of the host. Studies in germ-free mice have revealed that, compared with specific pathogen-free animals, germ-free mice have significantly reduced IgA-secreting plasma cells and Tregs in the lamina propria [13–15]. Applying this concept to human health may suggest that the lack of gut microbes may show a significant reduction in IgA levels. Furthermore, a recent study revealed that IgA levels in feces increased significantly after prebiotic treatment with diminished expression of pro-inflammatory factors in the mesenteric lymph nodes and Peyer's patches [14]. These findings suggest the positive impact of the commensal microbiota on the intestinal mucosal immunological balance.

Mucosal and systemic immunocompetence is influenced by the dynamic interactions of the microbiome with environmental factors. The study on lipopolysaccharide (LPS)-induced *Lactobacillus kefiri* treated mice showed a significant decrease in pro-inflammatory mediators (IL-6 and granulocyte-macrophage colony-stimulating factor) [14]. *Bacteroides fragilis* can produce polysaccharide A that has anti-inflammatory properties inhibiting IL-17 formation and increasing the activity of Tregs.

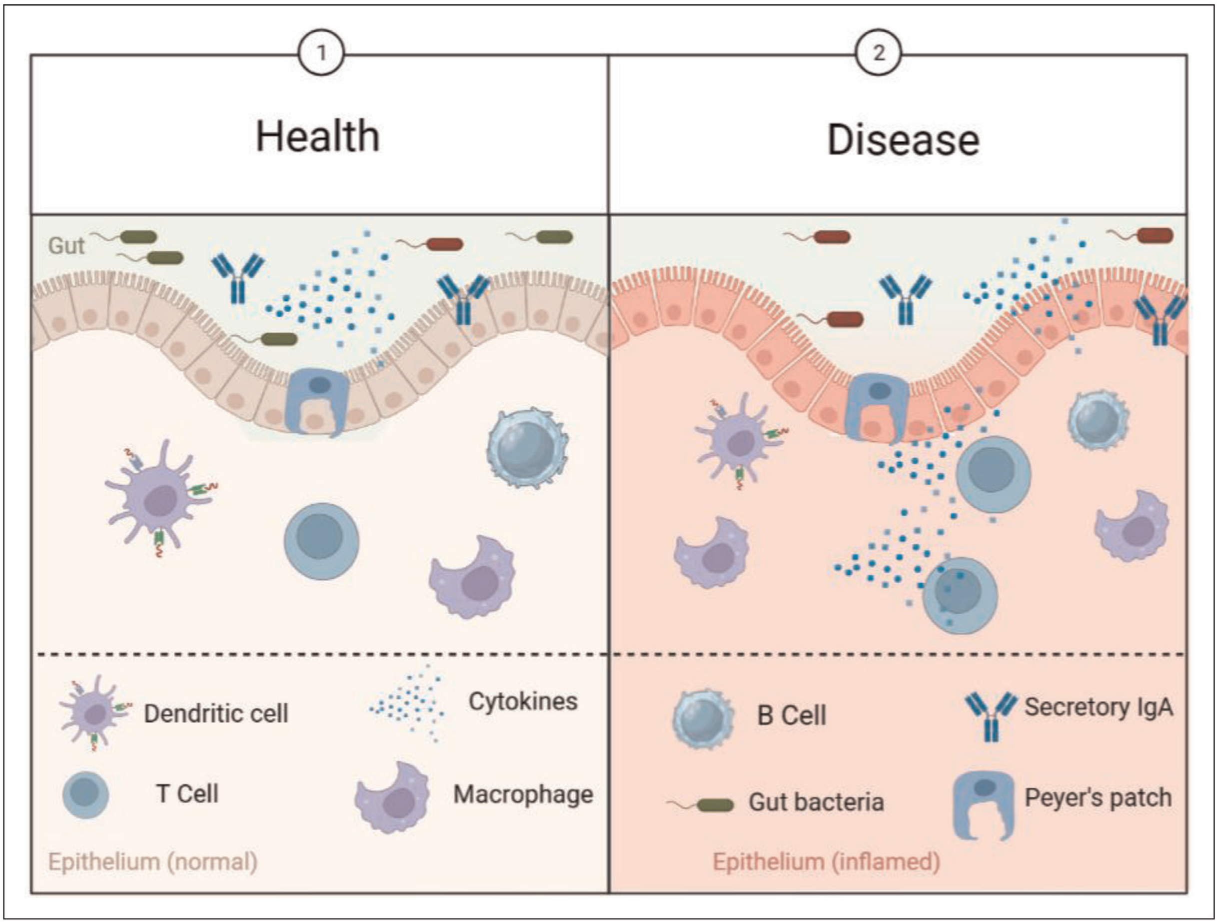

FIGURE 1. Conceptual diagram of immune responses in healthy [1▪] and dysbiotic [2] gut.

Polysaccharide A regulates CD4$^+$ T cell transformation toward Foxp3+Tregs in a TLR2-dependent manner. Tregs then produce anti-inflammatory cytokine (IL-10) in response to the defense against inflammatory injuries [16–18]. These studies showcase that the microbiome interaction with the host helps in maintaining immune homeostasis.

Dysbiosis and mucosal immunity alterations

Gastrointestinal dysbiosis is used to describe a change in the number and diversity of intestinal microbiota resulting in disease states [19▪▪]. Several factors can lead to dysbiosis, such as poor nutrition, stress, environmental factors (e.g., smoking, physical activity), or specific diseases (such as inflammatory, autoimmune, and chronic conditions). Drug use (i.e., antibiotics, anticancer drugs) and medical and surgical procedures can also contribute to dysbiosis [20].

Diet can change the composition and diversity of gut microbiota along with metabolites. For example, early in life, the gut microbiome is enriched in genes involved in digesting the oligosaccharide found in breast milk. After the introduction of solid foods, the metagenome would be enriched with genes targeting the metabolism of polysaccharides and vitamins [21]. Eating a vegetarian diet is linked to our health, the diversity of gut microbiota species, and the predominance of Firmicutes vs. Bacteroidetes [22].

Lifestyle also has significant effects on the gut microbiota, although with fewer published data. Activities such as smoking and lack of exercise tend to alter the gut microbial composition in humans [23]. Chronic cigarette smoking significantly alters the bacteria community structure and activity in the gut [24]. Smoking alters the oral microbiome by significantly reducing the levels of *Proteobacteria* while enriching *Atopobium* and *Streptococcus* [25]. In addition, stress can decrease *Bacteroides* but increase the *Clostridium* genus in the gut, which can adversely affect gut immunity [26]. Multiple preclinical studies have reported an association between stress and gut microbiota, but the same was not studied in humans [27,28].

Antibiotics have serious effects on gut microbiota, resulting in decreased bacterial diversity.

The potency, mechanism of action, dose, duration of administration, and pharmacokinetics of antibiotics can explain the extent of implications on gut dysbiosis [29]. For example, administration of fluoroquinolones and beta-lactams over 7 days has been shown to reduce microbial diversity by 25% and reduction in the core phylogenetic microbiota was from 29 to 12 taxa [30]. Even low doses of antibiotics can affect the gut microbiota during maturation, and reduce the immune response, potentially leading to significant changes in host metabolism and an increased risk for obesity [31,32]. Treatment with vancomycin results in a decrease in *Bacteroidetes*, *Ruminococcus*, and *Faecalibacterium*, but an increase in *Proteobacteria* [33]. Antibiotics cause gut mucosal breakdown, and thereby the acquisition of new bacteria that have the resistance gene, which undergoes horizontal transfer across the range of microbiome, thus resulting in antimicrobial resistance [29].

Microbial dysbiosis is associated with mucosal disruption, epithelial tight junction dysregulation, altered number and functions of Paneth cells, and intestinal permeability resulting in increased bacterial exposure [34,35]. Consequently, activated macrophages increase the production of proinflammatory cytokines such as tumor necrosis factor, IL-6, IL-23, and IL-12. Neutrophils secrete various intracellular granule components, which increase inflammation. Antigen-presenting dendritic cells stay in Peyer's patches or migrate to the mesenteric lymph nodes, wherein they present antigens to naive $CD4^+$ T cells with proliferation and differentiation into T-effector subsets, such as Th1, Th2, and Th17 cells [36]. Chemokine receptors and integrins are upregulated by Th1 and Th17 cells, which facilitate them to enter the systemic circulation and move to the intestinal tissue and secrete the relevant pro-inflammatory cytokines [37]. Increase in ILC1, ILC2, and ILC3 subsets, which are produced by pro-inflammatory cytokines and IgG-secreting plasma B cells during inflammation [38]. Tissue-resident memory cells (T_{RM}) are produced in addition to distinct subpopulations of effector T cells and Tregs in the gut mucosa [39]. T_{RM} cells are located near the epithelial compartment and lamina propria are responsible for the direct recognition of antigens, killing infected cells, the increase of an innate immunity response, and the recruitment of circulating memory T cells [40,41].

DYSBIOSIS AND HUMAN DISEASES

The gastrointestinal tract and its microbiome are inextricably linked, and any disruption of this symbiotic relationship can have detrimental consequences for both. Any alteration in the microbial composition can lead to unfavorable outcomes, including the development of a variety of diseases [42]. Numerous studies have been conducted to identify correlations between a variety of microbial species and the disease, as well as to construct hypotheses linking dysbiosis to the causes of various pathological conditions.

Gastrointestinal disorders

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, are immune disorders with dysbiotic microbiota. Recent studies suggest alteration of intestinal extracellular vesicle proteins may mediate host-microbiota interactions in pediatric IBD [43,44]. IBD patients show altered stool microbiota with loss of beneficial bacteria and enrichment of virulence factors [44]. Fecal samples by 16 s rRNA gene NGS reveal increased *Paraprevotellaceae* and *Porphyromonas* proportions in IBD dogs compared with healthy controls [45]. Individual differences in the host genome and gut microbiota may impact health, with high genetic risk individuals having a decreased *Roseburia* genus and a lower α diversity in ileal Crohn's disease compared with those with colonic Crohn's disease [46]. Gut microbiota signatures play a crucial role in the prognosis and IBD disease activity. Zhou *et al.* [47] show similar gut microbial alteration patterns among Chinese and Western populations, with increased *Actinobacteria* and *Proteobacteria* and decreased *Firmicutes*, relating to IBD severity. Altomare *et al.* [48] suggest that gut mucosa-associated microbiota better discriminates IBD differential patterns from healthy controls. FMT therapy may be a potential treatment for IBD in pediatric Crohn's disease and ulcerative colitis patients. Knoll *et al.* [49] found reduced species richness and diversity in autologous feces of children with ulcerative colitis compared with family donors. A study found that gut microbiota in elderly individuals with *Clostridioides difficile* infections (CDIs) have higher *Lactobacillus* and *Clostridia* diversity, while lower *Bacteroides*, *Prevotella*, and *Bifidobacteria* diversity. Prebiotics or probiotics maintain beneficial intestinal microbe diversity, potentially preventing or delaying infections [50,51]. In 2017, Mcllroy *et al.* [52] summarized the results of probiotics treatment studies in IBD, which showed inconclusive outcomes. Multiple randomized, controlled clinical trials (RCTs) investigating FMT as an induction treatment in patients with mild to moderate ulcerative colitis activity demonstrated promising outcomes for a limited number of participants [53–55]. Meta-analysis of FMT usage in the pediatric IBD population showed improved safety and efficacy compared to the adult population [56]. Two FMT products were recently approved by the U.S. FDA, namely, RBX-2660 in November 2022 and SER-109 in April 2023 for management of recurrent CDI in patients 18 years or older [57▪▪,58▪▪]. Gut microbiota modification is under intense research as an adjunct management strategy for several diseases.

Recent research indicates that bacteriophage may be essential for the restoration of gut microbial balance and to prevent disease progression. Phase 1 study showed that targeted therapy of *Klebsiella pneumoniae* associated IBD with bacteriophage decreased gut inflammation [59▪]. Various ongoing bacteriophage treatment RCTs are conducted in adults to monitor phage safety, and efficacy and improve clinical outcomes (NCT03269617, NCT04511221, NCT03808103, and so on). The bacteriophage therapy can be implemented as a standalone phage treatment, combined with FMT, or through genetically engineered phages [60▪].

Hematopoietic stem cell transplantation (HSCT) is used to treat a wide range of hematologic malignancies, and immunodeficiencies. One of the most serious complications of allogeneic HSCT is acute graft-versus-host disease (aGVHD), which causes high mortality and morbidity [61,62▪▪]. Increasingly, research suggests that aGVHD is closely linked to the gut microbiome [63–65]. In 2016, a study was conducted on aGVHD patients treated with FMT showed improved gastrointestinal systems, and it was linked to increased effector regulatory T cells [66]. DeFilipp *et al.* [67] reported that FMT treatment in allo-HSCT patients changes the microbiome diversity. A prospective cohort study was performed in refractory GI-GVHD patients, and they were treated with FMT along with antibiotics. The study reported that antibiotic usage hindered the microbiota diversity and lead to therapeutic failure [68]. These studies suggest that FMT may be an effective treatment option for GVHD; however, further research is necessary to confirm its long-term safety and effectiveness through RCTs.

Mental health

The gut-brain axis, bidirectional communication between the central nervous system and gut microbiota, has been linked to gastrointestinal and extragastrointestinal diseases, including anxiety and depression [69]. Prebiotics promote the growth of beneficial bacteria in the gut. Probiotics are beneficial bacteria and yeast, when consumed in an adequate amount, promotes good health. Probiotics prevent stress-induced synaptic dysfunction in neurons, potentially reducing damage and reducing ACTH and corticosterone levels in rats [70,71]. Study shows probiotics reduced cortisol levels and improved psychological effects in healthy volunteers, similar to antidepressants [72]. In mice, prebiotics offers anxiolytic and antidepressant effects to improve stress-induced microbiota changes by stabilizing *Bifidobacteria* and *Lactobacilli* populations [73]. Growing research indicates that gut microbiome may play a significant role in altering the metabolism of L-dopa in Parkinson's disease patients. Parkinson's disease showed improvement in motor and nonmotor symptoms at 6 months after treatment with FMT [74]. A pilot clinical study used FMT to treat cognitive impairment in patients with dementia by altering gut microbiome, and the results showed improvement in cognitive function in these patients [75▪]. There is a necessity to conduct additional RCT studies to evaluate FMT effectiveness and safety in neurodegenerative diseases.

Metabolic disorders

Gut microbiota co-evolved with humans, impacting host responses and potentially contributing to metabolic diseases such as obesity, diabetes, and fatty liver disease [76]. Two large meta-genomic studies show that individuals with type 2 diabetes mellitus (T2DM) have lower butyrate-producing *Clostridiales* and greater proportions of butyrate-free *Clostridioides*, suggesting the protective role of butyrate-producing bacteria [77,78]. A high-fat diet increases gut permeability and reduces tight junction protein expression in mice's intestinal epithelial cells [79]. Gut barrier disruption in high-fat diet-induced or genetically obese mice caused an increase in gut permeability and leakage of lipopolysaccharides into portal blood circulation [80–82]. Modulating gut microbiota with antibiotics or prebiotics improves gut permeability, reduces inflammation and metabolic endotoxemia, and alleviates glucose intolerance [83]. Metformin has been found to decelerate aging in *Caenorhabditis elegans* worms by altering *Escherichia coli* metabolism in the nematode's gut [84]. Further research is needed to fully understand the antiaging effects of metformin and its potential implications on human health and aging.

Autoimmune disorders

Altered gut microbiota may contribute to autoimmune diseases through molecular mimicry, intestinal mucosa permeability, host immune response, and antigenic mimicry [85]. A study reveals decreased *Ruminococcaceae* and increased *Proteobacteria* in SLE patients in northeastern China, characterized by decreased bacterial richness, lower *Firmicutes/Bacteroidetes* ratio, and increased *Bacteroides* species abundance in fecal samples [86]. Indole-3-carbinol mediates aryl hydrocarbon receptor activation, affecting macrophages in SLE patients by decreasing proinflammatory and overexpression of anti-inflammatory cytokine expression [87]. Ankylosing spondylitis patients have diminished biodiversity ratios and bacterial-fungal interkingdom networks were altered. The gut microbiota is characterized by increased *Proteobacteria*, reduced *Prevotella*, *Megamonas*, and *Fusobacterium* [88].

CONCLUSION

The gut microbiota represents a dynamic ecosystem with profound implications for human health and disease. Understanding the intricate relationship between gut microbiota and various clinical conditions opens new avenues for therapeutic interventions. Harnessing the therapeutic potential of the gut microbiota may revolutionize healthcare by providing novel strategies for disease prevention, management, and personalized medicine in the future.

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Conflicts of interest

There are no conflicts of interest.

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