

Role of intestinal microbiota and metabolites in inflammatory bowel disease

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Abstract

Objective: The metabolites produced by the gut microbiota are of interest to scientists. The objective of this review was to provide an updated summary of progress regarding the microbiota and their metabolites and influences on the pathogenesis of inflammatory bowel disease (IBD).

Data sources: The author retrieved information from the PubMed database up to January 2018, using various combinations of search terms, including IBD, microbiota, and metabolite.

Study selection: Both clinical studies and animal studies of intestinal microbiota and metabolites in IBD were selected. The information explaining the possible pathogenesis of microbiota in IBD was organized.

Results: In IBD patients, the biodiversity of feces/mucosa-associated microbiota is decreased, and the probiotic microbiota is also decreased, whereas the pathogenic microbiota are increased. The gut microbiota may be a target for diagnosis and treatment of IBD. Substantial amounts of data support the view that the microbiota and their metabolites play pivotal roles in IBD by affecting intestinal permeability and the immune response.

Conclusions: This review highlights the advances in recent gut microbiota research and clarifies the importance of the gut microbiota in IBD pathogenesis. Future research is needed to study the function of altered bacterial community compositions and the roles of metabolites.

Keywords: Inflammatory bowel disease; Metabolite; Microbiota

Background

Inflammatory bowel disease (IBD) is a term used for a group of complex chronic relapsing inflammatory diseases that damage the gastrointestinal tract. IBD is highly prevalent in western countries; however, owing to the rapid increase in its incidence and its prevalence in Asia, IBD is gradually emerging as a global epidemic spreading in both developed and developing countries.^[1-4]

Although IBD is generally considered to be associated with dietary patterns, genetic susceptibility, and abnormal immune and environmental factors, the detailed pathogenesis of IBD still remains to be uncovered.^[5-7] In recent years, the gut microbiota is likely to be the most important environmental factor in the pathogenesis of IBD. Approximately 160 significant bacteria among the

1000 to 1150 species of bacteria colonize the human intestinal tract.^[8] The commensal microbiota can protect the host against the colonization of opportunistic pathogens and can participate in the metabolism of food and the production of energy to supply essential nutrients and degrade indigestible compounds.^[9,10] Moreover, the commensal microbiota also contributes to the formation of the intestinal architecture and provides immunomodulatory functions.^[11,12] It has been indicated that both the microbiota and their metabolites affect the health of the host gut.^[13] These vast numbers of metabolites are first synthesized by the gut microbiota and then are transferred to the host, where they play essential roles in the homeostatic control of the host's health system. Increasing numbers of metabolites have been identified and functionally characterized in IBD research.^[14]

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Herein, we discuss the most recent findings focusing on the associations among IBD, the gut microbiota, and their metabolites, which may serve as pathophysiological factors in IBD. The potential applications of microbiota-centered biomarkers and therapeutic approaches for human IBD are also summarized.

Alteration of the Gut Bacterial Community Composition in IBD

Bacteria have been widely used for thousands of years in food and fuel production, drug discovery, the chemical industry, and human disease research. To date, less than 2% of bacterial organisms can be cultured in laboratory conditions.^[15] With the development of next-generation sequencing, communities of microbiota can be identified via 16S rRNA amplicon and shotgun metagenomic sequencing. Other multiomic technologies such as metatranscriptomics, metaproteomics, and metabolomics are also widely used to identify gut microbiota and improve understanding of their functional characteristics.^[16,17]

Mucosal dysbacteriosis usually occurs in both inflamed and noninflamed areas in IBD patients. Although how the affected parts of inflamed areas differ from the noninflamed parts is controversial, a remarkable change in the composition of the gut microbiota is observed in IBD patients.^[18,19] Several scientists have concluded that alterations in the microbiota composition are associated with IBD,^[20,21] and there is a consensus that bacterial biodiversity decreases along with changes in the relative abundance of specific bacterial groups, genera, or species.

Alteration of biodiversity

The biodiversity of feces/mucosa-associated microbiota is diminished in IBD patients.^[22] *Firmicutes* and *Bacteroidetes*, which are the predominant phyla of the healthy human gut microbiome, are depleted in IBD patients, whereas the phyla of *Proteobacteria* and *Actinobacteria* are elevated.^[23,24]

A decrease in the probiotic microbiota

Probiotics are “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.”^[25] There are many potential probiotic bacterial genera, such as *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*, whose composition in the gut microbiota is significantly diminished in IBD-active patients and IBD-inactive patients.^[22] Many bacterial genera have been studied, and two major genera are discussed and summarized below.

Faecalibacterium (F.) prausnitzii appears to be particularly underrepresented in intestinal samples and mucosa from IBD patients with Crohn disease (CD) or ulcerative colitis (UC).^[26] IBD-associated dysbiosis is characterized by a decrease in the ratio of *F. prausnitzii* to *Escherichia (E.) coli*. The well-studied butyrate producer *F. prausnitzii* is one of the most abundant bacteria in the healthy human intestinal microbiota, accounting for approximately 5% of

the total fecal microbiota. It belongs to the specific subgenus *C. leptum* of *Clostridium*, and, on the basis of numerous lines of reported evidence, *F. prausnitzii* has been proposed to contribute as a marker of, and a key player in, human intestinal health.^[27-29]

Another notable bacterium is *Bacteroides*. The average scale of *Bacteroides* in the intestinal microbiota community is significantly lower in CD and UC patients than in healthy controls, in both the active and the remission phase. Even among different stages of CD and UC, the mean level of *Bacteroides* is lower in the active phase than in the remission phase.^[30]

Increase in pathogenic microbiota in IBD

Although no definite relationship between the pathogenic microbiota and IBD has been established, the onset of risk of IBD can be triggered by specific pathogenic bacteria.^[31]

Mycobacterium avium subspecies *paratuberculosis*, which is broadly detected in the intestines of CD patients, can colonize the ileal mucosa of CD patients and is specifically correlated with CD.^[32] A mucosal biopsy study has shown that adherent-invasive *E. coli* are enriched in CD and UC patients compared with healthy controls.^[33] Additional studies have revealed that the onset risk of IBD increases after *Salmonella* or *Campylobacter* infection.^[34,35] Another group of invasive and adherent bacteria is *Fusobacterium*, a colonocyte-invading pathogenic bacterium that is found more prevalently in the IBD gut microbiota. Recent studies have shown that *F. nucleatum* strains isolated from inflamed biopsy tissue of IBD patients displayed significantly more invasive activity in a Caco-2 cell invasion assay than did strains isolated from the healthy tissue of either IBD or control patients.^[36]

Bacteria as a Biomarker of IBD

Profiling the intestinal microbiota has become a novel diagnostic tool in IBD disease treatment. Deep sequencing and Genome Analyzer map (GA-map) dysbiosis testing can uncover dysbiosis in irritable bowel syndrome and IBD patients and provide insight into a patient's intestinal microbiota.^[37] Fecal microbial profiles are used to differentiate between active and remission CD and highlight the potential of the fecal microbiota as a noninvasive tool for monitoring disease activity in CD.^[38] A molecular marker (csep1–6bpi) from *Campylobacter concisus* has been identified to be associated with active CD.^[39] Moreover, further evidence has revealed the potential of fecal microbiota as a useful noninvasive biomarker in monitoring the treatment of IBD. *Faecalibacterium* has been reported to be a potential biomarker for successful ustekinumab therapy in antitumor necrosis factor alpha refractory CD patients.^[40]

Microbiota as a Therapy Target in IBD

The two current primary therapeutic methods that utilize targeted microbiota are probiotics and fecal microbiota transplantation (FMT).^[41] Although the use of probiotics

as a therapeutic intervention has been reported, therapies involving probiotics usage have many limitations. The efficacy of probiotics in CD is not sufficient, a finding inconsistent with the effect on UC.

VSL#3 probiotics have a significant effect in patients with UC. Similarly, the combined administration of *Lactobacillus* probiotic and prebiotics has a significant effect only in patients with UC. A combination of three bacteria, *Saccharomyces boulardii*, *Lactobacillus*, and VSL#3 probiotics have also shown a trend toward improving CD. In children with IBD, the combination of *Lactobacillus* with VSL#3 probiotics has also shown a significant effect. Probiotics can benefit IBD treatment, especially with combined administration of probiotics for UC therapy.^[42]

FMT is well tolerated and effective for *Clostridium difficile*-infected IBD patients and may even prevent relapse in patients who previously underwent a colectomy. However, in a larger patient series, the cure rate using FMT in IBD patients was somewhat lower than that in patients without IBD, and FMT may induce an IBD flare to 25% among non-IBD-infected patients.^[43,44]

Roles of Metabolites From Microbiota in IBD

The microbiome colonized in the cecum and colon can produce undigested dietary fiber, proteins, and peptides, and can also synthesize, modulate, and degrade a large number of bioactive metabolites, some of which are critical signaling molecules contributing to human health in the gut and other organs.^[45] Alterations in the microbial composition can result in changes in the bacterial metabolome, which is generated in the gut and is dependent on microbial-producing activity. Microbiota-derived metabolites including short-chain fatty acids (SCFA), tryptophan, and other small molecules, have drawn considerable attention in IBD studies.

SCFA

SCFA are a group of fatty acid compounds with an alkyl chain shorter than six carbons. *F. prausnitzii* and *Ruminococcus bromii* are two dominant bacteria involved in butyrate production. They produce undigested dietary fiber, which is used as the source material to produce many SCFAs in the intestines.^[46,47] These small fatty acid molecules, including formic acid, acetic acid, propionic acid, butyric acid, valeric acid, acetate, and propionate, are mainly found in both the small and the large intestines, whereas butyrate is found in the colon and cecum.^[48] Usually, these SCFAs are beneficial to the gut, for example, by enhancing the intestinal barrier,^[49] providing abundant energy to the gut epithelial cells,^[50] and inhibiting inflammation.^[51] A disordered gut microbiota causes a decrease in butyrate production that is associated with IBD.^[52]

The butyrate production of some butyrate-producing bacteria is dramatically reduced in UC patients, thus resulting in a SCFA decrease in the colonic lumen in UC.^[53] Oral butyrate may improve the efficacy of oral mesalazine in curing active UC disease,^[46] and treatment with a diet that increases SCFA in IBD patients can also ameliorate colitis.^[54]

Tryptophan

Tryptophan is an essential amino acid that is necessary for humans. It is a substrate that can be incorporated into bioactive compounds with critical physiological functions during biosynthesis.^[55] Tryptophan deficiency can cause the development of IBD or aggravate disease activity.^[56] Indole derivatives originating from tryptophan in bacteria are also essential small molecules for health maintenance.^[57] As a first step in understanding the tryptophan degradation pathway, indoleamine 2,3-dioxygenase (IDO) was found to be responsible for the conversion of tryptophan and other indole derivatives to kynurenine.^[58] IDO expression in cells can vary according to disease activity,^[59] and locally high expression of IDO may provide a promising antiinflammatory mechanism to counterbalance the tissue-damaging effects of activated T cells, which infiltrate the colonic mucosa in IBD.^[60,61] Interestingly, plant-derived indole compounds have been used in traditional herbal medicine to treat IBD, thus supporting the importance of the kynurenines interacting with aryl hydrocarbon receptor and their actions on the immune system.^[62,63]

Mechanisms of bacteria in IBD

Increasing intestinal permeability may trigger the onset and relapse of IBD by inducing defects in primary barrier function. Bacteria can affect barrier function by regulating apoptosis among intestinal epithelial cells, synthesizing critical proteins for tight junctions, or affecting the mucus layer.^[64]

Another important mechanism is related to the regulation of the human immune system. Emerging evidence suggests that the host immune system can recognize gut bacterial metabolites other than pathogen-associated molecular patterns, and the recognition of these small molecules substantially affects the host immune response as well as disease and inflammation in the gut and beyond.^[65]

Conclusions

In summary, IBD is associated with dysbiosis of the gut microbial community and its metabolites. Recent progress in gut microbiota research has clarified the importance of the gut microbiota in IBD pathogenesis. The microbiota and their metabolites play pivotal roles in IBD by affecting intestinal permeability and the immune response. However, the use of the microbiota as a biomarker to monitor the development of IBD and the specific strains needed to induce or treat IBD require further investigation. The mechanism of bacterial community dysbiosis remains unclear, and the function of altered bacterial composition and the roles of the metabolites must also be further studied.

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Conflicts of interest

None.

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