Interplay of intestinal microbiota and mucosal immunity in inflammatory bowel disease: a relationship of frenemies

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Abstract: Inflammatory bowel diseases (IBDs), including ulcerative colitis and Crohn's disease, are chronic inflammatory disorders of the gastrointestinal tract. With in-depth studies on the mechanisms of the initiation and development of IBD, increasing lines of evidence have focused on the intestinal microbiota in the pathogenesis of IBD. The imbalance between the host and intestinal microbiota induces dysregulated immune response in intestinal mucosa and plays a pivotal role in the initiation of disease and ongoing bowel destruction. This review focuses on recent advances in intestinal microbiota regulation of mucosal immune response as well as novel approaches based on intestinal microbiota alterations in the diagnosis and evaluation of therapeutic response in IBD.

Keywords: diagnosis, immune response, inflammatory bowel disease, microbiota, therapeutic response

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Introduction

The gut microbiome is maintained in a state of mutual benefit and symbiosis with the host under physiological conditions and encodes a variety of functional genes, which enrich the human genome. Gut microbes, together with intestinal epithelial barrier and immune cells, form the complex intestinal microecosystem and perform two-sided functions, which do not merely contribute to systemic metabolism but also impact intestinal homeostasis. The intestinal microbes inhabit the surface of the lumen, which are mainly composed of plenty of bacteria, viruses, fungi, and parasites. The number of bacteria has been proved amount to about 10^{14}, which is almost tenfold of human cells. The total mass of intestinal bacteria is about 0.2 kg, accounting for 60% of the dry mass of the stool, and there are more than 50 phylotypes and about 1100 species.[1] Among them, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* form a major part of the gut microbiota, whereas the frequencies of *Proteobacteria* and *Fusobacteria* are correspondingly lower. The formation of a homeostatic microbial spectrum is closely associated with sex,[2] maternal health status,[3–5] the modes of childbirth (vaginal delivery or Cesarean delivery),[6] the diet composition in early childhood,[6,7] antibiotic use,[7] and contact with pets.[2,3] These factors at discrete stages display significant functions in gradually forming a balanced and harmonious state of the organism's microbial community. Previous studies have demonstrated that the intestinal microbial diversity of infants under 1 year of age proliferates and tends to be stable by the age of 3.[8,9] The complexity of the intestinal microbiota (number of taxa and functional genes) usually reaches the levels of adult before puberty. However, it is still different in taxonomy and function from adults. Generally, the number of *Bacteroides* is maintained at a relatively high level, whereas *Bifidobacterium* is lower.[10] Moreover, various environmental factors such as smoking, air pollution, hygiene habits, psychological stress, diets, and drugs have been proven to be involved in modulating the composition of intestinal microorganisms.[11]

The intestinal microbiota interacts with the host physiological process to assist in

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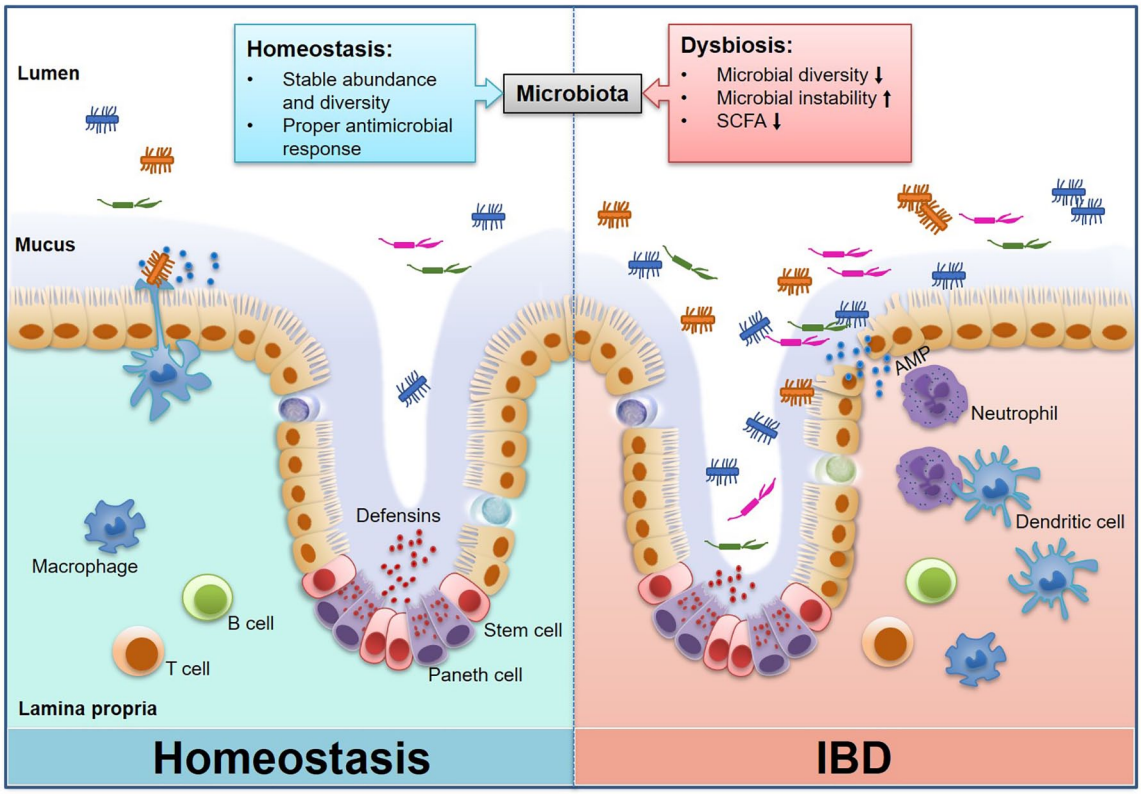

Figure 1. Interaction between intestinal microbiota and host immune response in normal and IBD states. Gut microbes play an essential role in maintaining the intestinal mucosal immune homeostasis, including the maintenance of intact intestinal mucosal barrier and moderate immune response to antigens. Disturbances in the abundance and diversity of intestinal microorganisms drive impaired function of the host intestinal immune system, and thus become a potential cause of a series of intestinal and systemic diseases including IBDs.
IBD, inflammatory bowel disease.

carbohydrate and amino acid metabolism,[12] energy harvest and storage from the diet,[13] protection against epithelial cell damage,[14] and induction of intestinal angiogenesis.[15] Previous studies have demonstrated an increase of susceptibility to food allergy in germ-free (GF) mice,[16] and antibiotic-treated wild-type mice, devoid of microbiota, also have an increased susceptibility to food allergy.[17] In addition, the early exposure to microbial antigens and microorganism colonization modulates host intestinal immune system development,[18] while microbial dysbiosis is generally considered to be associated with intestinal and systemic diseases, such as inflammatory bowel diseases (IBDs) (Figure 1), allergy, cancer, and metabolic abnormalities. In this review, we summarize the new concept on the relationship between intestinal microbiota and mucosal immunity in IBDs.

Unique microbial signatures in IBD

A retrospective study has demonstrated that antibiotic use during pregnancy and childhood significantly increases the risk of very early onset of IBD,[19] suggesting that the dysbiosis of intestinal microbiota is associated with the initiation of IBDs. An analysis of the intestinal microbiota within patients with IBDs also reveals a prominent alteration in their microbial spectrum, with reduced diversity [50% in Crohn's disease (CD) and 30% in ulcerative colitis (UC)] and increased microbial instability.[20,21]

Alternations of microbiota in patients with CD

Actinobacteria and *Proteobacteria* have been found to significantly increase in fecal samples, especially the more adherent and invasive Enterobacteriaceae, which have been detected in new-onset of patients with CD.[22] On the

contrary, *Bacteroides* and *Firmicutes* have been observed to be markedly decreased, and particularly, the *Lactobacillus* capable of producing short-chain fatty acids (SCFAs) is notably reduced in these patients.[20] Further analysis on fecal microbiota of patients with CD reveals a significant increase in Enterobacteriaceae. Consistently with the data from patients with CD, a subsequent murine colitis model also illustrates that tungstate could ameliorate the inflammatory responses *via* inhibiting the excessive growth of Enterobacteriaceae.[23] Another study has demonstrated that *Faecalibacterium prausnitzii* is significantly reduced in the stools of patients with CD,[24] which has been proven to be closely associated with disease relapse. Moreover, evidence has further demonstrated that *F. prausnitzii* transplanted into a murine model of chronic colitis could relieve inflammatory response in the intestinal mucosa. Importantly, the treatment with food-grade *Lactococcus lactis*, which delivers a plasmid encoding microbial anti-inflammatory molecules expressed by *F. prausnitzii*, elicits a significant remission of experimental colitis in mice, suggesting that anti-inflammatory substances secreted by *F. prausnitzii* play an essential role in regulating intestinal inflammatory response.[24]

Alternations of microbiota in patients with UC

Microbial products in the feces of patients with UC have been confirmed to promote intestinal mucosal inflammation, while dendritic cells from healthy volunteers stimulated by filter-sterilized fecal solution from feces of patients with UC and co-cultured with naïve T cells have been observed to profoundly increase the proportion of differentiated type 2 helper T (T_H2) cells, which are closely related to the severity of the disease.[21] Numbers of *Bacteroides* and *Candida* have been observed to significantly increase in feces of patients with UC.[25,26] Another analysis has reported that less butyrate is synthesized by *Clostridium* in the luminal flora of patients with UC, suggesting a protective role of *Clostridium* in the initiation of UC.[27] Moreover, a fecal metabolomics study further revealed an increased frequency of symbiotic *Escherichia coli* during intestinal inflammation, and its respiration and formate oxidation have been proved to participate in the occurrence of microbial imbalance and intestinal inflammatory response.[27] In addition, the alterations of microbiota are also present in patients with defects in the IBD susceptibility genes. For instance, intestinal microbiota analysis of patients with defects in caspase recruitment domain family member 9 (*CARD9*), one of the admitted IBD susceptibility genes, has shown that the microbes capable of metabolizing tryptophan, such as *Lactobacillus*, are not adequate to process enough metabolites as aromatic hydrocarbon receptor (AhR) ligands. Analysis of fecal metabolites in patients with UC with *CARD9* gene deficiency has also shown that the reduced density of tryptophan-derived indole derivatives elicits downregulated activation of the indole-related AhR signaling pathway and decreased interleukin (IL)-22 production,[28] which contribute to the recovery from colitis.

Microbiota dysbiosis is associated with the disease progression of IBD

Previous studies have demonstrated that several microorganisms are involved in the pathogenic progression of IBD.[29,30] A retrospective study has shown that the levels of *Clostridium difficile, E. coli O157*, *Salmonella* and *Staphylococcus aureus* toxins are significantly increased in the sera of patients with IBD with a longer course of disease, and that the concentrations of these toxins are also significantly higher in patients with active IBD than those in patients with IBD in remission or healthy volunteers,[31] indicating that the toxins produced by the intestinal microbiota may be directly absorbed through the damaged intestinal mucosal barrier into the circulation and participate in the procession of IBD. Therefore, the serum levels of bacterial toxins can be used as indicators of IBD progression. In addition, we have also found that a large number of bacteria is capable of binding IgA or IgG in the fecal samples of patients with active IBD, and that the contents of soluble IgA and IgG in feces are significantly increased in patients with active IBD compared with healthy controls, which are also positively correlated with the disease activity of patients with IBD.[32]

Summary

Numerous studies have shown that there is a prominent variation in the diversity, abundance, and metabolite of intestinal microbes between patients with IBD and healthy individuals. The variation has been proven to contribute to the disease progression of IBD *via* impacting the immune response in gut mucosa. Taken together,

these findings allow us with the possibility to further study the etiology, pathology, diagnosis and treatment of IBD using the intestinal flora as a breakthrough.

The Janus-faced properties of intestinal microbiota in gut immunity of IBD

Essential role of microbiota in initiating immune responses in gut mucosa

Microbiota has been proved to play an essential role in the formation of a well-developed immune system. Previous data have shown that there are diminished regulatory T (T_{reg}) cells,[33] fewer supervised $CD4^+CD8\alpha\alpha^+$ intraepithelial lymphocytes,[34] impaired innate lymphoid cell function[35] and increased susceptibility to bacterial infection in GF mice. Aside from the effects on immune response in mice, relevant data on human study have also shown that the intestinal microbiota displays various properties in promoting proper immune development.[36,37] Microbial exposure at the juvenile stage has been found to contribute to the development of human T_H cells, especially the establishment of intestinal T_H2 immune response.[33] Immune disorders caused by insufficient microbial exposure are considered to be one of the etiological agents of IBD. Epidemiological studies have also shown that underexposure of microbiota in juveniles is associated with immune-related diseases in adulthood, called the 'hygiene hypothesis',[38] and that the underlying mechanisms may be ascribed to the inhibition of the excessive production of IgE from intestinal microbiota.[39] An animal experiment has further demonstrated that colitis fails to occur when $CD4^+CD45RB^{high}$ T cells from GF mice are reconstituted into Rag-$1^{-/-}$mice, suggesting that the intestinal microbiota is involved in the activation of colitogenic $CD4^+$ T cells and the induction of colitis.[40] After oral administration of antibiotics for 7 days, abnormal activation of macrophages is also observed in the intestinal mucosa, which further affects the intestinal mucosal immune homeostasis, especially the immune response regulated by $CD4^+$ T cells.[41] Therefore, the intestinal bacterial antigens are involved in a variety of immune responses in the intestinal mucosa.

Role of microbiota-derived antigens in inducing T-cell differentiation in gut mucosa

Evidence has shown that certain microbiota-derived antigens play an immune-mediated destructive or protective role in inducing the differentiation of mucosal $CD4^+$ T cells into T_H1, T_H17 or T_{reg} cells. Transplantation of *Bacteroides fragilis* into GF mice induces the differentiation of T_H1 cells.[41,42] Polysaccharide (PSA) produced by *B. fragilis* is a prerequisite for the induction of T_H1 cell differentiation, which also acts as a ligand for Toll-like receptor 2 on the surface of $CD4^+$ T cells and participates in the activation of $CD4^+$ T cells.[41,42] In addition, segmented filamentous bacteria (SFB) have the potential to induce the differentiation into T_H17 cells in the intestine.[43] Once SFB infiltrates into the mucus layer and contacts with the intestinal epithelial cells (IECs), expression of T_H17-related genes is observed to increase in IECs, which is in line with an enhanced proliferation and differentiation into T_H17 cells.[44] Other intestinal commensal microbes such as altered Schaedler flora could also promote the differentiation of mucosal $CD4^+$ T cells into T_H17 cells.[45] However, some intestinal commensal microbes, such as *Clostridium nucleus* and *Peptostreptococcus*, could induce intestinal $CD4^+$ T cells to differentiate into T_{reg} cells.[46] The underlying mechanisms whereby the microbiota-derived antigens induce the differentiation into T_{reg} cells may be ascribed to the induction of IL-10 by intestinal $CX3CR1^+$ phagocytic cells through the symbiotic antigens.[47]

Role of microbiota-derived antigens in maintaining intestinal homeostasis

The intestinal commensal microbiota is supposed to interact with intestinal immune cells and maintain the homeostasis as well as a stable internal environment. Previous studies have shown that PSA from the outer membrane vesicles (OMV) of *B. fragilis* activates dendritic cells and induces the release of IL-10 in T_{reg} cells, which functions as an anti-inflammatory mediator in regulating intestinal mucosal immunity.[48] Further, this process mainly depends on cellular autophagy-related proteins ATG16L1 and NOD2.[49] Consistently, dendritic cells in the intestinal mucosa of patients with CD with ATG16L1 or NOD2 gene deficiency fail to recognize the OMV, which causes reduced T_{reg} cell differentiation and decreased IL-10 secretion. In addition, intestinal commensal bacteria are also able to maintain a

stable intestinal innate immune response by limiting excessive colonization and growth of pathogenic bacteria.

Summary

These published data have indicated that the intestinal microbiota prominently affects both the initial development of the immune system and the immune responses in intestinal mucosa under physiological or pathogenic conditions. However, the exact roles of intestinal microbiota in regulating homeostasis in gut mucosa are still not fully understood and need further investigation in the future.

Relevance of intestinal microbial metabolites to regulating immune responses in gut mucosa

Role of microbiota-derived SCFAs in regulating intestinal mucosal immune responses

Immune regulation by microbial metabolites (e.g. SCFAs) on intestinal homeostasis has been paid more attention to better understand the pathogenesis of IBD.[50,51] SCFAs mainly consist of acetic acid, propionic acid and butyrate, which are produced by intestinal bacteria through decomposing dietary fiber and play a critical role in intestinal immunity. SCFAs have been confirmed to regulate cell differentiation, proliferation, and exocrine functions *via* binding G protein-coupled receptors (GPR) 41, GPR43, and GPR109 on the surface of immune cells and IECs. They promote the production of acetyl-CoA and regulate metabolic receptors in B cells, leading to an increase of immunoglobulin production (e.g. IgA, IgG) in gut mucosa and a profound promotion of B cells to differentiate into plasma cells.[52] In agreement with these findings, we have also found a decreased secretion of soluble IgA (sIgA) and poor capacity of binding bacteria in the intestinal lumen from Gpr43$^{-/-}$ mice, along with a decrease of intestinal IgA^{+} B cells. After feeding wild-type mice with acetic acid, sIgA and intestinal IgA^{+} B cells are observed to increase in feces. On the contrary, the levels of sIgA in feces and the frequencies of IgA^{+} B cells in intestinal mucosa are not found to recover in Gpr43$^{-/-}$ mice, indicating that acetic acid could induce sIgA secretion by intestinal B cells in a GPR43-dependent manner.[53] Another study has also demonstrated that *Clostridium*, including clusters IV, XIVa, and XVIII, elicits a robust differentiation of mucosal CD4^{+} T cells into CD4^{+}Foxp3^{+} T_{reg} cells by producing SCFAs.[54] Furthermore, SCFAs are also observed to facilitate intestinal mucosal CD4^{+} T cells to produce IL-10, which is reduced in Gpr43$^{-/-}$CD4^{+} T cells, suggesting that SCFAs modulate CD4^{+} T-cell differentiation and promote IL-10 production through the GPR43-mediated pathway.[55,56]

Role of microbiota-derived indole derivatives in regulating intestinal mucosal immune responses

Accumulating lines of evidence have demonstrated that intestinal microbiota metabolizes tryptophan into indole derivatives, including indole, indole acetic acid, indole propionic acid, and indole acetaldehyde, which have been shown to be involved in intestinal homeostasis.[57] Analysis of intestinal microbial metabolites in patients with IBD has revealed that reduced tryptophan metabolites (indole, indole propionic acid, and indole acetaldehyde) decrease the biological activity of AhR and cause intestinal inflammatory damage.[58] Indole metabolites have been demonstrated to promote IECs to express IL-10R1 and reinforce the intestinal mucosal barrier, while tryptophan kinase-mutant *E. coli* fails to induce the expression of IL-10R1 in IECs.[55] Animal studies also subsequently proved that the indole metabolite could activate the IL-10 signaling pathway and elicit attenuation of colitis.[55] In addition, transplantation of fecal microbiota from *Card9*$^{-/-}$ or *Il-22*$^{-/-}$ mice into GF recipients promotes the initiation of colitis, while the administration with three *Lactobacillus* strains (*L. murinus* CNCM I-5020, *L. reuteri* CNCM I-5022, *L. taiwanensis* CNCM I-5019) competent in metabolizing tryptophan, or the remediation with AhR agonists [6-formylindolo (3,2-b) carbazole (Ficz)] elicits the recovery of IL-22 and amelioration of colitis.[28] Interestingly, the underlying mechanisms of the colitis induced by fecal microbiota from *Card9*$^{-/-}$ or *Il-22*$^{-/-}$ mice are found to be associated with a reduced indole content in the intestinal stool. Other protective effects of *Lactobacillus*, especially *L. murinus*, are associated with the induction of T_{reg} cells.[59] Therefore, dysbiosis, especially the loss of intestinal microbiota capable of modulating intestinal inflammation, has been extensively proved to contribute to the compromised homeostasis in intestinal mucosa. Furthermore, the administration of specific

microbiota, especially targeted therapy aiming at rectifying the microbial dysbiosis in patients with IBD, may provide a therapeutic approach in the management of disease.

Summary

Intestinal dysbiosis and alternations of microbial metabolites (such as SCFAs, indoles) have been proven to be involved in the pathogenesis of IBD. Studies on microbial metabolites may provide therapeutic approaches in the diagnosis and treatment of IBD.

Potentials of microbiota in evaluating clinical diagnosis, treatment and prognosis of IBD

Potential roles of microbiota in the diagnosis and assessment of disease activity of IBD

In recent years, accumulating data on intestinal microecology have been illustrated as a hot spot in the clinical translational study of IBD. Alterations of intestinal microbiota may provide new clues for evaluating clinical diagnosis, treatment, and prognosis of IBD. There are significant differences in the fecal microbial spectrum between patients with IBD and healthy donors, while fecal microbiota transplantation (FMT) in patients with IBD also needs to follow the selectivity of disease.[60,61] In a cohort study, they collected feces from 2045 patients with IBD for 16S rRNA analysis, and conspicuous microbial dysbiosis was found in patients with CD, including decreased diversity and abundance. They finally screened out eight types of microbiota to differentiate CD from other diseases, showing that *Faecalibacterium*, an unknown genus of *Peptostreptococcaceae, Anaerostipes, Methanobrevibacter* and an unknown genus of *Christensenellaceae* were abundant in the normal control group and patients with UC, while *Fusobacterium* and *Escherichia* were enriched in the feces of patients with CD. Furthermore, *Collinsella* was detected only in the feces of patients with UC. In addition, the accuracy rate distinguishing CD and non-CD diseases reached 77% when the fecal microbiota was used as the marker, with the sensitivity of 60% and the specificity of 68%. In addition, the accuracy rate identifying CD and UC was about 64%, with the sensitivity of 60% and the specificity of 94.8%.[62] Another cohort study collected the feces of 21 patients with remission CD, 17 siblings, and 19 healthy volunteers for microbial profile analysis. The results showed that the fecal microbiota of relatives of patients with CD had similar changes, and that the diversity was markedly decreased compared with healthy controls. Notably, *F. prausnitzii* was significantly decreased, along with a high risk of CD disease.[63] Taken together, these results may partially explain the phenomenon of family aggregation in IBD. Moreover, the levels of microbial metabolites such as SCFAs and indole metabolites in the stool of patients with IBD are significantly decreased,[64] which are found to be related to the changes in the intestinal microbial spectrum at the time of onset. Therefore, the alternations of microbial metabolites or microbial spectrum may be used as an indicator of clinical diagnosis and activity assessment of IBD.

Therapeutic approach of FMT in the treatment of IBD

Recently, numerous emerging therapeutic approaches have been applied in the treatment of IBD, including small-molecule inhibitors, monoclonal antibodies against pathogenic proinflammatory cytokines and chemokines, and FMT. With the in-depth understanding of intestinal microbiota, FMT has been implemented as a treatment strategy for several diseases, especially for the treatment of multiply recurrent *Clostridioides difficile* infection.[65] In a randomized controlled study of FMT for active UC, the response rate of the FMT-treated group (24%) at week 7 was significantly higher than that in the placebo group (5%), and the intestinal bacterial diversity of FMT-treated patients was significantly higher than controls.[60] A double-blind, controlled study of patients with active UC who received treatment with fecal enema from healthy volunteers demonstrated that the rate of steroid-free clinical remission and endoscopic remission in the FMT group was higher than that in the placebo group at week 8 [risk ratio = 3.6, 95% confidence interval (CI) 1.1–11.9, $p = 0.021$], and that the intestinal microbial diversity of patients with UC receiving FMT was also higher compared with that in the placebo group.[66] A randomized clinical trial of 8-week FMT in patients with active UC using anaerobically treated feces demonstrated that steroid-free remission was achieved in 32% patients (12 of 38) receiving mixed unrelated donor feces compared with 9% patients (3 of 35) receiving autologous feces (difference = 23%, 95% CI 4–42%, odds ratio = 5.0, 95% CI 1.2–20.1, $p = 0.03$).[67] The anaerobic

treatment of feces effectively avoided the loss of beneficial obligate anaerobic microbiota, such as *F. prausnitzii*, which is associated with better clinical remissions in patients with UC.[68] However, several limitations still prevent the clinical application of FMT for UC, including inconsistent clinical trial protocol, small sample size, and unstable efficacy. The efficacy of FMT is currently determined in the active phase of treatment in patients with UC, but the long-term tolerance or safety is still less predictable. However, the evidences are still not available on the efficacy of FMT in patients with CD.[69,70] A meta-analysis of FMT in patients with CD has demonstrated a clinical remission rate of 52% (95% CI 31–71%, $p = 0.063$, $I^2 = 52\%$) among 71 patients with CD receiving FMT.[71] Moreover, the only clinical trial referring to endoscopic remission in patients with CD showed no significant improvement at week 8 among the patients receiving FMT.[72] The prospect of FMT in the treatment of patients with CD is still modest giving to the current scanty research data.[73] In order to apply the introduction of FMT in clinical treatment for IBD, many questions still need to be solved, including the timing of FMT in patients, individual selectivity, dose of induce remission and long-term maintenance.

The application prospect of intestinal microbiota in IBD

Alterations of intestinal microbiota may be used to predict the therapeutic response in the treatment of IBD. A prospective study of anti-tumor necrosis factor-α in the treatment of UC has demonstrated that the intestinal microbiota before treatment shows less dysbiosis and higher abundance of *F. prausnitzii* in the responders than that in the nonresponders. Importantly, *F. prausnitzii* also increases in stool during induction therapy.[74] In another study of vedolizumab (i.e. anti-α4β7 monoclonal antibody) in the treatment of IBD, the α diversity of fecal microbiota in patients with CD who responded at week 14 was significantly increased, and the patients with an increased abundance of *Roseburia* and *Burkholderiales* species before treatment had higher efficacy.[75] Moreover, the intestinal microbiota could also predict the risk of postoperative complications and recurrence in surgically treated patients with IBD. *Rumenococcus gnavus*, *Bacteroides vulgatus*, and *Clostridium perfringens* were observed to increase in feces of patients with UC with pouchitis after ileal pouch-anal anastomosis, while Lacnospiraceae genera and *Roseburia* were markedly reduced.[76] After ileocolonic resection in patients with CD, microbiota changes in the small intestine and anastomotic region directly affected the recurrence of postoperative inflammatory reactions, while *F. prausnitzii* and *Ruminococcus gnavus* had been found to have protective roles in this process.[77] Another study on intestinal microbiota alterations of patients with CD after ileal resection has proven that the ileectomy elicited a reduction in the α diversity of ileal mucosa-associated microbiota. *Proteobacteria* (especially *Alphaproteobacteria*), Coribacteriaceae, and *Enterococcus* were found to be significantly increased, while *Firmicutes* (especially Lachnospiraceae) and Ruminococcaceae (especially *Eubacterium*, *Ruminococcus*, *Butyricoccus*, *Dorea*, and *Blautia*) were reduced. These changes were observed to be related to endoscopic recurrence and could be a predicted indicator of postoperative recurrence.[78]

Summary

With the in-depth study of intestinal microbiota, the microbial differences present in patients with IBD are expected to provide a novel approach for the diagnosis, treatment and prognosis of IBD. Although there are still some limitations that could not be ignored in the treatment of IBD through adjusting the composition of intestinal microbiota such as FMT. As our understanding of intestinal flora is getting more thorough, the proper treatment of IBD in virtue of intestinal microbiota will be just around the corner.

Conclusion

Intestinal microbiota plays a key role in regulating immune homeostasis in the enteric internal environment and interacts with mucosal various immune cells responsive to the initiation of IBD. Probing the roles of intestinal microbiota in the initiation and development of mucosal inflammation will provide a new theoretical basis to better understand the pathogenesis of IBD, and importantly, open a novel avenue for future clinical diagnosis, treatment, and prognosis.

Author contributions

ZL was responsible for conception, literature review and revising the manuscript. CH and HL drafted the manuscript and interpreted the results. All authors agreed to the final version.

Conflict of interest

The authors declare that there is no conflict of interest.

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