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REVIEW

Association between intestinal microbiota and inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), has emerged as a global disease with high incidence, long duration, devastating clinical symptoms, and low curability (relapsing immune response and barrier function defects). Mounting studies have been performed to investigate its pathogenesis to provide an ever-expanding arsenal of therapeutic options, while the precise etiology of IBD is not completely understood yet. Recent advances in high-throughput sequencing methods and animal models have provided new insights into the association between intestinal microbiota and IBD. In general, dysbiosis characterized by an imbalanced microbiota has been widely recognized as a pathology of IBD. However, intestinal microbiota alterations represent the cause or result of IBD process remains unclear. Therefore, more evidences are needed to identify the precise role of intestinal microbiota in the pathogenesis of IBD. Herein, this review aims to outline the current knowledge of commonly used, chemically induced, and infectious mouse models, gut microbiota alteration and how it contributes to IBD, and dysregulated metabolite production links to IBD pathogenesis.

KEYWORDS

dysbiosis, IBD model, intestinal microbiota, metabolites

1 | INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a non-infectious, chronic, and relapsing inflammatory disorder of the gastrointestinal tract in which the interactions among immune responses, barrier function, nutrition, and gut microbiome are involved.[1–3] CD can affect any segment of the gastrointestinal tract, from the mouth to the anus, with the terminal ileum and perianal regions being the most,[4,5] while UC is usually limited to the colon and rectum, especially in the distal colon and rectum.[6] Despite differences in diseased parts, these two diseases share partially overlapping pathological and clinical symptoms, including diarrhea, abdominal pain, cramping, rectal bleeding, weight loss, spontaneous remission, bloody stool, and relapsing inflammation.[7,8]

Epidemiological and observational studies indicate that IBD has become a global burden with rapidly increasing incidence and prevalence in both men and women in both industrialized countries and developing countries.[9,10] It is urgent to underline the exact pathogenesis of IBD to provide new insights for the prevention or treatment of this disease. Thus, mounting attempts have been made to understand the precise etiologies and pathogenesis of IBD.[11] Generally, it is accepted that genetic factors, intestinal microbiota, environmental factors, and immune responses play a key role in the initiation and/or progression of IBD.[12,13] Considering that microbiota and environmental factors may interact with genetic elements,[14] most identified susceptibility genes are involved in immune responses in the pathogenesis of IBD.[15,16] It is more practical to regulate IBD progress by targeting the intestinal microbiota.[17–19] Thus, in the current review, we mainly outlined an update of most used IBD mouse models, shifts in composition and functions of intestinal microbiota, and correlation between dysbiosis and IBD.

2 | COMPOSITION AND FUNCTIONS OF THE INTESTINAL MICROBIOTA

The mammalian gastrointestinal tract serves as a habitat for an enormous and complex community of microorganisms, including fungi, viruses, protozoans, and bacteria, termed as intestinal microbiota.[20,21] The community of commensal fungi, also called the mycobiota, is composed of 66 fungal genera and 184 fungal species in gastrointestinal tract of healthy individuals.[22] The number and abundance of fungi in the lower gastrointestinal tract is orders of magnitude smaller than that of bacteria.[23] Based on descriptive data in humans and mechanistic data in mice, recent insights have demonstrated that gut mycobiota are not only altered in gastrointestinal diseases such as IBD but also play a key role in maintaining intestinal homeostasis and modulating immune response.[24,25] Furthermore, growing evidence reported that gut fungi in patients with IBD contribute to the aggravation of the inflammatory response, leading to increased disease severity.[22,25] Nevertheless, the underlying mechanism of gut mycobiota contributing to IBD remains incompletely understood. Understanding the interaction among fungi, bacteria, and host immune response will help address the contribution of the mycobiota in IBD and develop novel approaches for protection and/or manage gastrointestinal disease.[22,26] Prokaryotic viruses (bacteriophages) and eukaryotic viruses in the gut together are termed as gut virome that is recognized as an essential part of the gut microbiome and play a vital role in the pathogenesis of multiple diseases.[27] Accordingly, enteric viruses are strongly related to intestinal inflammation evidenced by gut virome enriched from non-IBD, and noninflamed colon resections display anti-inflammatory effects.[28] Furthermore, a significant difference in virome between IBD patients and healthy individuals was observed.[29] Notably, the changes in virome composition reflected alterations in bacterial composition among IBD subjects, indicating interactions between enteric virus and intestinal bacteria.[30,31] Although viruses have been reported to be associated with IBD, mounting analyses are still needed to explore the accurate role of virus in the molecular pathogenesis of IBD because of the very limited literature, currently. Data regarding protozoans in IBD were omitted because of limited studies. Bacterial microbiota has always been the most abundant and studied component among the four intestinal microbial flora,[32,33] which is composed of 100 trillion microbial organisms, forming the essential part of the microbiota ecosystem.[34,35] The whole bacteria in the intestine comprise approximately 1000 species, most of which belong to the dominant phyla of Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria,[36,37] and other less are classified into Verrucomicrobia, Fusobacteria, and Cyanobacteria phyla.[38] The intestinal microbiota is less diverse at birth and develops into a highly complex one as it interacts more with diets,[39,40] which contain nutrients required for the symbiotic bacteria, pathogens, exogenous antigens, and toxins. In another aspect, the bacteria also exhibit differences both from mucosal to luminal and proximal to distal gradients along the whole intestine,[41] displaying substantial variations among individuals.[42] Here we comprehensively elucidate the alterations in the gut microbiota (intestinal bacteria) in IBD to provide crucial insight into investigation of the IBD pathogenesis.

The gut microbiota of healthy individuals has been reported to live in a symbiotic relationship and co-evolve with the host by providing crucial physiological functions, including nutrient digestion and absorption, development of the intestinal immune system, and host defense against exogenous pathogens.[43] Some bacteria of Bacteroidetes and Firmicutes phyla are capable of fermenting resistant starch or indigestible carbohydrates to generate short-chain fatty acids (SCFAs), which are major energy sources for the colonic epithelium and are reported to stimulate cell proliferation.[44,45] Other bacteria, such as Bacteroides, also participate in carbohydrate metabolism through degrading glycosyl transferases, glycoside hydrolases, and polysaccharide lyases.[46] Furthermore, it has also been reported that the intestinal microbiota is vital for lipid metabolism by activating lipoprotein lipase activity.[47,48] In addition, the gut microbiota metabolizes protein via its proteinases and peptidases in coordination with the host. Then, amino acid transporters, which are located at the cell wall, facilitate the entry of amino acids into the

bacteria, where they are metabolized as small signaling molecules or bacteriocins, or synthesized as microbial proteins.[49] Also, it is well known that members of intestinal bacteria can de novo synthesize and supply vitamins, such as vitamin K and most of the water-soluble B vitamins.[50]

A recent work has demonstrated that impaired immune system development was observed in germ-free (GF) mice,[51,52] while reconstruction of the microbial community or colonization of specific *Candidatus Arthromitis* restored the deficits and abnormalities,[53–55] which indicates the potential role of microbiota in immune system maturation. Consistently, other studies reported the modulatory role of SCFAs produced by intestinal bacteria on differentiation and expansion of regulatory T cells (Tregs),[56,57] reduced T helper 17 (Th17) cells in GF or antibiotic-treated mice,[58,59] as well as the role of intestinal bacteria on T-cell repertoires.[60] In addition, the GF animals are more susceptible to pathogen infections due to the immature mucosal immune system, which reveals that intestinal bacteria exert a profound impact on host defense, including, but not limited to, metabolism, ontogeny, and pathogen defense.[61] The commensal bacteria in the intestine inhibit pathogen infection by directly competing for nutrients,[62–64] or secretion of bacteriocins indirectly as mentioned earlier,[65,66] termed as the colonization resistance, which is another aspect of host defense directed by the intestinal microbiota.

3 | MURINE MODELS ARE USEFUL TOOLS FOR PATHOPHYSIOLOGY AND ETIOLOGY OF HUMAN IBD

Currently, though mounting evidence has demonstrated the valuable roles of dysbiosis in the pathogenesis of IBD, precise mechanisms of intestinal bacteria contributing to disease pathogenesis remain incompletely understood yet (Figure 1). With the development of current biotechnology in animal models, the complexity of IBD has been uncovered. Various murine models of IBD have been developed, including the chemically induced dextran sodium sulfate (DSS) model, 2,4,6-trinitrobenzenesulfonic acid (TNBS) model, and acetic acid model, and the *Citrobacter rodentium* (*C. rodentium*) model of infectious colitis has been utilized in an effort to provide further insights and develop more therapeutic options. In this review, we summarize the experimental animal models of IBD that are widely used, reproducible, and easy to operate, which may contribute to the identification of IBD pathogenesis process.

DSS is a synthetic sulfated polysaccharide with a variable molecular weight ranging from 5 to 1400 kDa.[67] Intestinal epithelial cells (IECs) exposed to DSS lead to the breakdown of mucosal integrity, resulting in the exposure of mucosal and submucosal immune cells to luminal antigens and finally erosions with complete loss of surface epithelium.[68,69] Continuous administration of 40–50 kDa DSS in drinking water leads to acute colitis, which shares similar symptoms with human UC.[69,70] The severity of DSS-induced colitis depends on its molecular weight, strain and sex of the mice, and microbial environment, especially the dosage and duration.[71] Modification of doses and timing allows modeling of different phases of colitis: the acute colitis usually develops for 5–7 days with the dose range of 1.5%–5%, while the chronic colitis needs continuous treatment of low concentrations for weeks or cyclical administration of DSS (Table 1). Furthermore, DSS model recovers spontaneously after the termination of DSS administration, which becomes another mouse model for exploring the mechanisms in recovery phase (Table 1).

TNBS has been defined as a hapten that binds to tissue proteins in the intestine and elicits a number of immunologic responses.[69] Dissolving in 40–50% ethanol is necessary for TNBS to induce colitis, of which alcohol is a prerequisite to break the mucosal barrier to facilitate the entry of TNBS into the lamina propria, where it haptenizes the localized colonic and gut microbial proteins to generate TNP-specific $CD4^+$ T cells.[72] Following studies identified the adapted immune responses with the activation of Th1, Th2, and

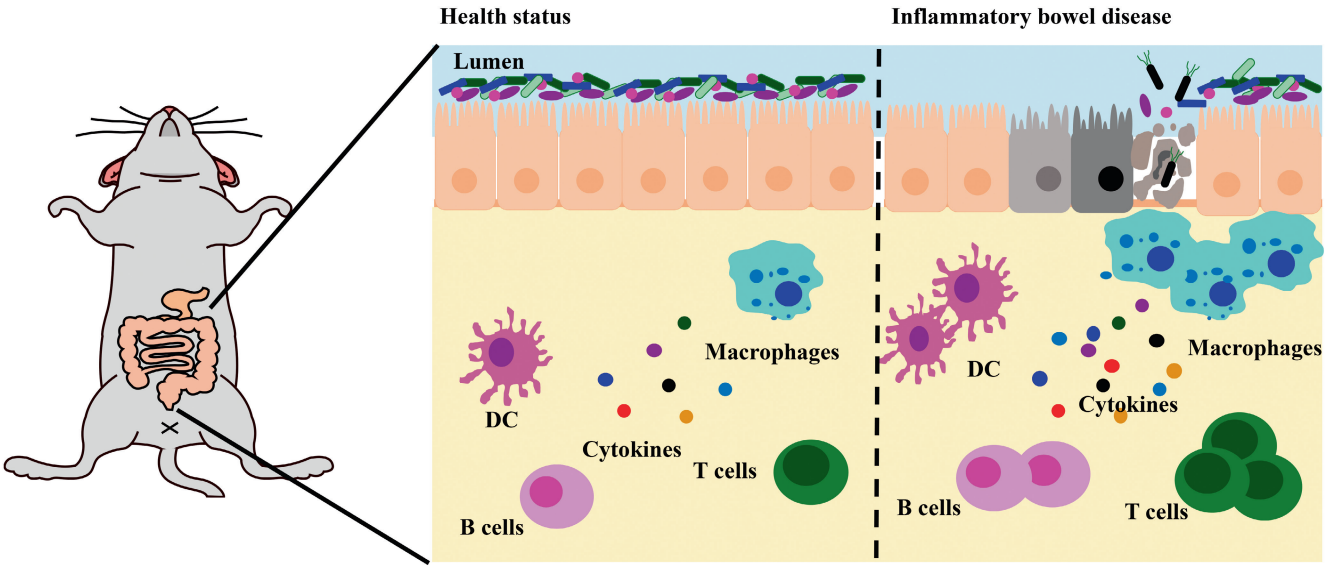

FIGURE 1 The role of intestinal epithelium, gut microbiota, and immune response in the pathogenesis of IBD.

TABLE 1 Murine models of IBD

Colitis models	Mechanisms	Procedures	References
DSS	Toxin to epithelial cells; breaks down mucosal integrity; exposure of immune cells	2%–5% DSS treatment for 5–7 days for acute colitis; low dose of DSS for weeks for chronic colitis; termination of DSS treatment for recovery phase	79,91–98
TNBS	Serves as a hapten and renders haptenization of intestinal proteins; elicits dysregulated Th cell immune response	3 and 1.5 mg in 50% ethanol for BALB/c; 2.5 mg in 50% ethanol for SJL/J; 2.5 mg in 50% ethanol for C3HeJ; 2 mg in 45% ethanol for C57BL/6	99–102
Acetic acid	Destructs colonic epithelium; activates NF-κB signal	1 ml of 5% acetic acid for Kuming and C57BL/6; 0.2 ml of 7.5% acetic acid for Swiss mice	78,79–103
C. rodentium	Forms A/E lesion; injects effector proteins	Orally administered with *C. rodentium*; combined use of DSS and *C. rodentium*	90,104–106

Abbreviations: DSS, dextran sulfate sodium; TNBS, trinitrobenzene sulfonic acid.

Th17 cells in response to TNBS exposure.[68] Thus TNBS-induced colitis comprises two forms of IBD and predominantly captures many features of CD.[73] The recommended dosage for the induction of acute colitis involves intrarectal injection of 0.5–40 mg once, and clinical symptoms may arise 5–7 days after rectal administration.[74] In addition, continuous intrarectal administration of TNBS is often used to develop chronic colitis model, characterized by increased mucosal thickness, loss of goblet cells, and infiltration of inflammatory cells.[75] In addition, strains of mouse should be considered as SJL/J, C3HeJ, and BALB/c are susceptible strains, whereas C57BL/6 and DBA/2 are resistant ones (Table 1).[72]

Acetic acid–induced colitis is easy to manipulate and is also commonly employed in IBD research, and the operational processor is quite similar to that of TNBS-induced colitis. Rectal administration of acetic acid–induced colitis shares common histopathological characteristics with those of UC patients, including transmural necrosis, edema, submucosal ulceration, and depletion of goblet cells,[76] which is another well-established mouse model for UC. Colitis was induced by rectal instillation of 1 mL of 0.9% saline-diluted acetic acid (4%–5%) with a catheter into the lumen of colon 4 cm proximal to the anus.[77] Mice were maintained in a supine Trendelenburg position for 30 s to prevent the leakage of the acetic acid solution.[78,79] Mucosal injury was related to the epithelia necrosis and edema, whose severity depended on the dose and duration of exposure time of acetic acid. Chemical destruction of colonic epithelium starts within 4 h and spontaneously heals within days in mice.[74] Inflammatory responses contribute to the aggravated colonic mucosal damage via activation of nuclear factor-κB (NF-κB) signal pathway, infiltration of immune cells, and subsequent release of pro-inflammatory cytokines and reactive oxygen species (ROS).[78] By contrast, the epithelial injury in the first 24 h is possibly induced by the protonated form of the acid, which liberates protons instead of immune responses,[77] which indicates that choosing a proper time point 24 h post-induction is crucial when exploring the immunologic mechanisms.[71]

C. rodentium, widely used as a model to study infection-induced colitis, is a gram-negative and mouse-restricted enteric pathogen belonging to the attaching and effacing (A/E) pathogen family, which also includes human enteropathogenic *Escherichia coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC).[80–82] The colonization process of A/E family pathogens is achieved by forming the A/E lesions: intimate adherence to IECs, effacement of the brush border microvilli, and reorganization of the host actin cytoskeleton to form pedestal-like extensions.[83] *C. rodentium*-induced colitis is one of the rare models of infectious colitis that has been extensively studied and characterized since the discovery and use of this bacterium.[84,85] In addition, *C. rodentium*-induced colitis is also an outstanding *in vivo* model to investigate host–pathogen interactions in human IBD,[81] as it shares 67% of its genes with both EHEC and EPEC, including locus of enterocyte effacement (LEE) pathogenicity island.[86] Upon forming the A/E lesions, *C. rodentium* serves as a pathogen by injecting effector proteins into host cell via the type III secretion system (T3SS), which is considered as the main pathogenesis of infection.[83] *C. rodentium*-induced colitis is casually established by oral administration, followed by a robust Th1/Th17 immune response,[83] thus leading to transmissible murine crypt hyperplasia (TMCH) primarily in the distal large intestine.[81,82] Some mice strains can spontaneously clear this bacterium and heal in 21–28 days post-infection,[81] whereas *C. rodentium* is fatal to other strains.[87,88] Commonly used colitis models of *C. rodentium* are summarized in Table 1.

The chemically induced models are widely used in IBD investigation for their convenience in conducting the experiments; however, they have self-limitations. Because the inflammatory responses come after the epithelium damage, this may not be a preferred model when exploring the dysbiosis as short-time colitis possibly cannot reflect true changes in intestinal microbiota in long-term IBD process.[89] The *C. rodentium*-induced colitis model is a rare model suitable for investigating host–pathogen immune interactions in the gut, which represents the TMCH without epithelial destruction.[90] In addition to the IBD models described earlier, there are also numerous mouse IBD models, such as the adoptive transfer and genetically deficient models.[69] These models, combined with the introduced ones in this section, have greatly facilitated the investigation of IBD.

4 | CORRELATIONS BETWEEN DYSBIOSIS AND IBD DEVELOPMENT

4.1 | Intestinal microbiota shifts as a consequence of IBD

Under normal physiological conditions, the intestinal microbial community plays an important role in maintaining gut homeostasis; nevertheless, this homeostasis can be altered by various stimulations, such as exogenous infections, antibiotic use, dietary antigens, and toxins.[107] Indeed, altered composition and diversity of the microbiota have been documented in the intestine of IBD patients as compared with healthy individuals before or after treatment.[34,108,109] IBD patients exhibited a reduction in α-diversity and abundance of Firmicutes compared to healthy individuals.[110] Besides, elevation in gut Proteobacteria and Bacteroidetes has been reported.[111,112] Clinical observation revealed that IBD patients exhibited the decrease in overall diversity, reduced abundance of bacteria with anti-inflammatory property, such as *Clostridium* groups IV and XIVa, *Bacteroides*, *Suterella*, *Roseburia*, *Bifidobacterium* spp., and *Feacalibacterium prausnitzii*, as well as enhanced abundance of colitogenic microbiota, including adherent invasive *E. coli*, *Pasteurellaceae*, *Veillonellaceae*, *Fusobacterium* spp., and *Ruminococcus gnavus*.[113,114] In particular, elevated abundance of *Pasturellaceae*, *Veillonellaceae*, *Neisseriaceae*, *Fusobacteriaceae* spp., and *E. coli* and reduced abundance of *Bacteroides*, *Clostridiales*, *F. prausnitzii*, *Roseburia* spp., *Blautia* spp., *Helicobacter pylori*, and *Ruminococcus* spp. were reported in CD patients (Table 2).[115,116] UC patients exhibited a less species diversity at all stages of the disease in comparison with healthy individuals.[117] It has been reported that an induction of *E. coli* and reduction of *F. prausnitzii* were also observed in UC patients, which is similar with CD patients.[118] Besides, UC patients displayed even higher inflammation and dysbiosis compared to those with CD.[119] Generally, later analysis showed that lower abundance of *Akkermansia muciniphila* (*A. muciniphila*), *Butyricicoccus pullicaecorum* (*B. pullicaecorum*), *Roseburia hominis* (*R. hominis*), and *Clostridium colinum* (*C. colinum*)[120,121] and higher abundance of *Fusobacterium* spp. were indicated in UC patients in comparison with healthy individuals (Table 2).[122]

Treatment with DSS resulted in a lower abundance of Bacteroidetes and Firmicutes, and a significant higher abundance of Proteobacteria.[123] Furthermore, decreased abundance of *Lactobacillus*, *Alloprevotella*, and *Lachnospiraceae_NK4A136_group* and increased abundance of *Bacteroides*, *Helicobacter*, *Akkermansia*, and *Desulfovibrio* were also found in DSS-treated mice (Table 2).[123,124] Reduced abundance of Bacteroidetes and increased abundance of Proteobacteria were observed in TNBS-treated mice, which are further characterized by increased abundance of *E. coli* and decreased abundance of *Lactobacillus johnsonii* (*L. johnsonii*).[125,126] In addition, reduced abundance of *Peptostreptococcaceae*, *Erysipelotrichaceae*, *Methylobacteriaceae*, *Sphingomonadaceae*, and *Lachnospiraceae* were reported in TNBS-treated mice (Table 2).[127] In acetic acid–induced mouse model of colitis, reductions in *Clostridia*, *Ruminococcaceae*, and *Clostridiales* and inductions of *Enterobacteria* were reported (Table 2).[128,129] Otherwise, little is known on the disrupted roles of acetic acid in colitis of mice. *C. rodentium* infection in mice resulted in decreased α-diversity of the microbiota and populations of *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, and *Clostridia*, as well as increased populations of *Fusobacterium* and *Enterococcus*.[130] Another study also observed reductions in the relative abundance of *Lactobacillus*, *Bifidobacterium*, *Alistipes*, *Turicibacter*, *Parabacteroides*, and *Alloprevotella*, as well as inductions of *Lachnospiraceae_NK4A136_group* in *C. rodentium*-infected mice (Table 2).[90] Dysbiosis in IBD patients and chemical-induced colitis in mice have been well documented in numerous studies; however, changes in specific taxa may be inconsistent, which may be affected by various factors, including gender, age, diets, and reared environment. Knowing the role of dysbiosis in the development progress of IBD will help with clinical therapeutic options based on intestinal microbiota. They have also contributed to the development of novel therapeutic options that selectively target dysbiosis in IBD.

TABLE 2 Intestinal microbiota shifts as a consequence of IBD

Types	Inductions	Reductions	References
CD	*E coli*, *Pasturellaceae*, *Veillonellaceae*, *Neisseriaceae*, *Fusobacteriaceae* spp.	*Bacteroides*, *Clostridiales*, *F. prausnitzii*, *Roseburia* spp., *Blautia* spp., *Ruminococcus* spp., *H. pylori*	115,116
UC	*E coli*, *Fusobacterium* spp.	*F. prausnitzii*, *R. hominis*, *C. colinum*, *A. muciniphila*, *B. pullicaecorum*	118,120–122
DSS	Proteobacteria, *Bacteroides*, *Helicobacter*, *Akkermansia*, *Desulfovibrio* Proteobacteria, *E. coli*	Bacteroidetes, Firmicutes, *Lactobacillus*, *Alloprevotella*, *Lachnospiraceae_NK4A136_group*	123,124
TNBS		Bacteroidetes, *L. johnsonii*, *Peptostreptococcaceae*, *Erysipelotrichaceae*, *Methylobacteriaceae*, *Sphingomonadaceae*, *Lachnospiraceae*	125–127
Acetic acid	*Enterobacteria*	*Clostridia*, *Ruminococcaceae*, *Clostridiales*	128,129
C. rodentium	*Lachnospiraceae_NK4A136_group*, *Fusobacterium*, *Enterococcus*	*Bacteroides*, *Bifidobacterium*, *Lactobacillus*, *Clostridia*, *Turicibacter*, *Parabacteroides*, *Alistipes*, *Alloprevotella*	90,130

Abbreviations: CD, Crohn's disease; DSS, dextran sulfate sodium; IBD, inflammatory bowel disease; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis.

4.2 | Intestinal microbiota is important in initiation and progression of IBD

As reviewed earlier, IBD commonly displays intestinal microbiota dysbiosis. However, understanding the dysbiosis of IBD patients and experimental colitis is insufficient to investigate the potential role of the microbiome in the development, progression, and treatment of IBD.[131] The relation of intestinal microbiota and IBD can be well defined by the disease activity, which is more evident in the colon than the small intestine and rectum where the bacterial populations are relatively lower.[132] Most experimental IBD models only develop in the presence of conventional microbiota, while GF mice fail to develop intestinal inflammation.[133] It is agreed that constant gut dysbiosis seems to be a key factor in the aggravation of the inflammation,[134,135] which has been supported by a higher abundance of adherent and invasive bacteria Fusobacteria. *Fusobacterium* spp. were reported to be higher in the colonic mucosa of UC patients when compared with healthy controls.[33,122] Following research studies revealed the ability of *Fusobacterium* spp. in adhering to and invading colonic epithelial cells, as well as positive correlation of this bacterium with the severity of IBD, indicating the role of *Fusobacterium* spp. in fascinating the progression of IBD and may be a useful biomarker for gastrointestinal disease.[136,137] In addition, colonization with mucosa-associated microbes of UC patients was able to increase the susceptibility to DSS-induced colitis instead of inducing spontaneous colitis in gnotobiotic BALB/c mice.[138] In other studies, mice that received fecal microbiota transplantation (FMT) from UC patients with low Firmicutes were more sensitive to colitis compared with those received from fecal or synthetic ecosystems enriched in Firmicutes.[139,140] Besides, elevated proinflammatory gene expression profile was reported in GF mice colonized by disturbed intestinal microbiota isolated from CD patients causing inflammatory tissue damage.[133,141]

Except for these human clinical trials and corresponding experimental data, accumulating evidence obtained from mouse models provides convincing data for a key causal role of intestinal microbiota in the development of intestinal inflammation.[142] For example, an underlying mechanism of epithelium damage in DSS and acetic acid–induced colitis is attributed to dysregulated immune responses activated by resident microbiota,[89] which indicates the key causal role of commensal microbiota in the onset of IBD.[143] Of note, GF and antibiotic-treated mice provide an excellent research tool to investigate the role of bacteria in colitis. A study concluded that GF mice treated with 1% DSS resulted in severe colitis in comparison with conventionally reared mice, whereas GF mice treated with 5% DSS failed to induce colitis lesions, but induced moderate colitis in conventional mice.[144] The contradictory result may be attributed to the high toxicity of DSS to GF mice and death prior to colitis development because of the massive bleeding into the intestinal lumen. In line with this phenomenon, the latter study showed that GF and antibiotic-treated mice were highly susceptible to epithelial injury in DSS-induced colitis.[145] In contrast, mice treated with 4-antibiotic regimen for 2 weeks showed a sustained reduction in microbial diversity and 54% decrease in colitis severity when compared with control mice.[146] Correspondingly, the sustained protective effects of antibiotics were also confirmed by the FMT experiment, which showed that recipients of stool from antibiotic-treated mice exhibited a significantly lower colitis score than those from untreated controls.[146] One speculation of this protective effect is attributed to a less colitogenic microbiota. In fact, contribution of intestinal microbiota in DSS-induced colitis has always been conflicted. In addition, some researchers demonstrated that DSS-induced colitis normally developed in the absence of bacteria,[147] while moderate inflammatory responses of DSS colitis in GF conditions were also observed.[148] The reason for these discrepancies remains uncovered. Despite the intense interest in the role that dysbiosis may play in the immunopathogenesis of chronic intestinal inflammation, it is currently not clear whether dysbiosis is a cause or consequence of chronic tissue inflammation.

The crucial role of intestinal microbiota can also be validated in genetically susceptible mice as most spontaneous rodent models of IBD require the presence of bacteria to develop disease. For example, mice deficient in core 1-derived *O*-glycans (TM-IEC *C1galt1*$^{-/-}$) developed spontaneous colitis with a diminished mucus layer and reduced goblet cell population, but failed to develop inflammation in GF conditions.[149–151] Consistent with this, interleukin-2 (IL-2) knockout mice spontaneously developed a UC-like colitis with a 50% mortality,[152] while it failed to develop inflammation when kept in GF conditions.[153] In line with these literatures, a previous report revealed that mice deletion of IL-10 spontaneously developed colitis when maintained in conventional conditions, while GF *IL-10*$^{-/-}$ mice had no sign of colitis or immune system activation when kept in GF conditions.[154] Nevertheless, antibiotic treatment has distinct effects in spontaneous colitis in *IL-10*$^{-/-}$ mice according to two reports, one of which showed antibiotic therapy attenuated colitis in *IL-10*$^{-/-}$ mice,[155] while the other showed antibiotics exacerbated colitis in *IL-10*$^{-/-}$ mice by affecting the microbiota composition, Tregs population, and SCFAs production.[156] Eliminating all the intestinal microbiota or not may be the interpretation for this conflicting observation as the author suggested.[156] Moreover, transferring of disrupted microbiota of CD patients to GF *IL-10*$^{-/-}$ mice elicited the development of severe colitis, which further showed the promoted role of intestinal bacterial in IBD-prone mice.[133] All the updated references summarized here seem to reveal the roles of dysbiosis in promoting onset or development of IBD regarding the decreases of probiotics and increases of pathogens, and future research studies are needed to pay more attention to the prevention of dysbiosis in IBD progression especially on some novel candidate bacteria.

4.3 | Dysregulated metabolite production links to IBD pathogenesis

Numerous studies revealed that the disrupted metabolites as a result of dysbiosis are linked to the pathogenesis of IBD.[157,158] There is

an increasing interest in SCFAs, main metabolites of gut microbiota, given its potentially important role in remission of chronic inflammation.[159] SCFAs, including acetate, propionate, and butyrate, are produced by fermenting non-digestible and non-absorbable dietary fiber and resistant starches.[160,161] SCFAs function as energy sources of colonic epithelial cells[162] and exhibit anti-inflammatory effects by binding to G-protein-coupled receptors (GPRs).[163] Butyrate is the most important anti-inflammatory SCFA by suppressing NF-κB and interferon-γ (IFN-γ) signaling,[164,165] enhancing peroxisome proliferator-activated receptor-γ (PPARγ) activation,[166] and regulating proliferation and differentiation of Tregs.[167] *Faecalibacterium prausnitzii* (*F. prausnitzii*) is one of the most abundant butyrate-producing species, which is significantly decreased in ileal biopsies of CD patients and in the colon of UC patients.[168,169] Furthermore, restoration of *F. prausnitzii* is associated with maintenance of clinical remission of UC, and a low proportion of *F. prausnitzii* has been associated with higher risk of IBD recurrence.[169,170] The mucin-degrading bacteria *A. muciniphila* is able to produce acetate and propionate during this degradation process.[160,171] Furthermore, the decreased population of *A. muciniphila* and concentrations of acetate, propionate, and butyrate have been observed in DSS-treated mice, whereas FMT enriched with *A. muciniphila* and SCFAs improved DSS-induced colitis in mice.[172] Correspondingly, the administration of *A. muciniphila* could ameliorate DSS-induced UC-type colitis in mice.[173] Accordingly, decreased populations of SCFA-producing bacteria and SCFA production have been reported in IBD patients and colitis mice,[172,174,175] while supplementation of SCFA-producing bacteria or SCFAs showed a positive improvement in colitis, which indicated the high relations of gut microbiota metabolites with IBD development. In contrast, some metabolites, such as hydrogen sulfide, may have opposite effects against SCFAs in IBD development, which can disrupt the use of butyrate in colonocytes.[176] In addition, literature reported that proinflammatory sulfur-reducing bacteria were more abundant in IBD patients compared to healthy individuals,[177] which reduce sulfur and sulfur-containing compounds to hydrogen sulfide.[178] Otherwise, cultured supernatant of *F. varium* isolated from UC patients containing high concentrations of *n*-butyric acid is toxic to Vero cells, and rectal administration of enema containing the cultured supernatants caused UC-like colonic mucosal inflammation in mice,[179] which indicates that some metabolites in dysbiosis can promote onset or progression of IBD.

5 | CONCLUSIONS

The well-characterized and commonly accepted pathogenesis of IBD includes genetic susceptibility, intestinal microbiota, environmental factors, and immune responses, among which the intestinal microbiota attracts more spotlights as it can be easily modified by genetic and environmental elements and activate host immune responses. Much of the current knowledge to date has identified the indispensable roles of the microbial community within the host, including, but not limited to, nutrient metabolism, intestinal immune system development, and host defense. Nevertheless, the homeostasis regarding the commensal bacteria and the host can be easily disrupted by various exogenous stimuli, resulting in dysbiosis, including changes in diversity, compositions, and metabolites, resulting in overactivated immune responses. In this scenario, intestinal dysbiosis and dysregulated immune responses co-occur in IBD patients and colitis mice, which lead to the remaining question: Is dysbiosis a cause or effect of IBD? It can be evidenced without any doubt by large numbers of clinical research studies that dysbiosis happens as a common phenomenon in IBD patients. In addition, there is robust evidence in all mouse models that showed the altered intestinal microbial flora in the development and progression of colitis. By using the FMT biotechnology in GF, humanized gnotobiotic, and genetically modified mice, dysbiosis as a trigger of colitis seems to be revealed. Owing to these available data, the intestinal microbiome is rapidly becoming the evolving target for diagnosis, prognostication, and treatment of IBD. Future research studies or therapeutic options targeting microbe-based therapeutics will be critically important, even though prospective studies still need to be undertaken.

AUTHOR CONTRIBUTIONS

Yunchang Zhang, Ye Sun, and Ning Liu wrote the main manuscript text. Xuemeng Si designed and produced figures of manuscripts. Ling Yang and Hui Wang were involved in writing, review, and editing. All the authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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