Association between intestinal microbiota and inflammatory bowel disease

Yunchang Zhang¹ | Xuemeng Si²,³ | Ling Yang⁴ | Hui Wang⁴ | Ye Sun⁵ | Ning Liu²,³

¹Ministry of Agriculture and Rural Affairs, Institute of Feed Research, Chinese Academy of Agricultural Sciences, Beijing, China
²State Key Laboratory of Animal Nutrition, Department of Animal Nutrition and Feed Science, China Agricultural University, Beijing, China
³Beijing Advanced Innovation Center for Food Nutrition and Human Health, Department of Nutrition and Health, China Agricultural University, Beijing, China
⁴Department of Food and Bioengineering, Beijing Vocational College of Agriculture, Beijing, China
⁵Institute of Medical Laboratory Animal Science, Chinese Academy of Medical Sciences & Comparative Medical Center, Peking Union Medical College, Beijing, China

Correspondence
Ye Sun, Institute of Medical Laboratory Animal Science, Chinese Academy of Medical Sciences & Comparative Medical Center, Peking Union Medical College, Beijing 100021, China. Email: sunye1224@163.com
Ning Liu, Beijing Advanced Innovation Center for Food Nutrition and Human Health, Department of Nutrition and Health China Agricultural University, Beijing 100193, China. Email: nuli982390@163.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: nos. 32000082 and 31625025; Project funded by China Postdoctoral Science Foundation, Grant/Award Number: 2022M713405; R&D Program of Beijing Municipal Education Commission, Grant/Award Number: KM202212448002; and the 111 Project, Grant/Award Number: B16044

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. 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, while UC is usually limited to the colon and rectum, especially in the distal colon and rectum. 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.

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. 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. 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. Considering that microbiota and environmental factors may interact with genetic elements, most identified susceptibility genes are involved in immune responses in the pathogenesis of IBD. It is more practical to regulate IBD progress by targeting the intestinal microbiota. 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. 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. The number and abundance of fungi in the lower gastrointestinal tract is orders of magnitude smaller than that of bacteria. 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. Furthermore, growing evidence reported that gut fungi in patients with IBD contribute to the aggravation of the inflammatory response, leading to increased disease severity. 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. 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. Enteric viruses are strongly related to intestinal inflammation evidenced by gut virome enriched from non-IBD, and noninfamed colon resections display anti-inflammatory effects. Furthermore, a significant difference in virome between IBD patients and healthy individuals was observed. Notably, the changes in virome composition reflected alterations in bacterial composition among IBD subjects, indicating interactions between enteric virus and intestinal bacteria. 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, which is composed of 100 trillion microbial organisms, forming the essential part of the microbiota ecosystem. The whole bacteria in the intestine comprise approximately 1000 species, most of which belong to the dominant phyla of Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria, and other less are classified into Verrucomicrobia, Fusobacteria, and Cyanobacteria phyla. The intestinal microbiota is less diverse at birth and develops into a highly complex one as it interacts more with diets, 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, displaying substantial variations among individuals. 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. 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. Other bacteria, such as Bacteroidetes, also participate in carbohydrate metabolism through degrading glycosidases and polysaccharide hydrolases, and poly saccharide lyases. Furthermore, it has also been reported that the intestinal microbiota is vital for lipid metabolism by activating lipoprotein lipase activity. In addition, the gut microbiota metabolizes protein via its proteases 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. 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.

A recent work has demonstrated that impaired immune system development was observed in germ-free (GF) mice, while reconstruction of the microbial community or colonization of specific Candidatus Arthromitis restored the deficits and abnormalities, 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), reduced T helper 17 (Th17) cells in GF or antibiotic-treated mice, as well as the role of intestinal bacteria on T-cell repertoires. 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. The commensal bacteria in the intestine inhibit pathogen infection by directly competing for nutrients, or secretion of bacteriocins indirectly as mentioned earlier, 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. 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. Continuous administration of 40–50 kDa DSS in drinking water leads to acute colitis, which shares similar symptoms with human UC. 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. 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. Furthermore, DSS model recovers spontaneously after the termination of DSS administration, which becomes another mouse model for exploring the mechanisms in recovery phase.

TNBS has been defined as a hapten that binds to tissue proteins in the intestine and elicits a number of immunologic responses. 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. 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.
Th17 cells in response to TNBS exposure.\textsuperscript{68} Thus TNBS-induced colitis comprises two forms of IBD and predominantly captures many features of CD.\textsuperscript{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.\textsuperscript{74} In addition, continuous intrarectal administration of TNBS is often used to develop chronic colitis models, characterized by increased mucosal thickness, loss of goblet cells, and infiltration of inflammatory cells.\textsuperscript{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).\textsuperscript{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,\textsuperscript{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.\textsuperscript{77} Mice were maintained in a supine Trendelenburg position for 30 s to prevent the leakage of the acetic acid solution.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{77} which indicates that choosing a proper time point 24 h post-induction is crucial when exploring the immunologic mechanisms.\textsuperscript{71}

\textit{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 \textit{Escherichia coli} (EPEC) and enterohemorrhagic \textit{E. coli} (EHEC).\textsuperscript{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.\textsuperscript{83} \textit{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.\textsuperscript{84,85} In addition, \textit{C. rodentium}-induced colitis is also an outstanding in vivo model to investigate host-pathogen interactions in human IBD,\textsuperscript{81} as it shares 67% of its genes with both EHEC and EPEC, including locus of enterocyte effacement (LEE) pathogenicity island.\textsuperscript{86} Upon forming the A/E lesions, \textit{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.\textsuperscript{83} \textit{C. rodentium}-induced colitis is casually established by oral administration, followed by a robust Th1/Th17 immune response,\textsuperscript{83} thus leading to transmissible murine crypt hyperplasia (TMCH) primarily in the distal large intestine.\textsuperscript{81,82} Some mice strains can spontaneously clear this bacterium and heal in 21–28 days post-infection,\textsuperscript{81} whereas \textit{C. rodentium} is fatal to other strains.\textsuperscript{87,88} Commonly used colitis models of \textit{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 epithelial 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.\textsuperscript{89} The \textit{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.\textsuperscript{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.\textsuperscript{89} These models, combined with the introduced ones in this section, have greatly facilitated the investigation of IBD.

### Table 1: Murine models of IBD

| Model          | 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                   |
| \textit{C. rodentium} | Forms A/E lesion; injects effector proteins                              | Orally administered with \textit{C. rodentium}; combined use of DSS and \textit{C. rodentium} | 90,104–106                  |

Abbreviations: DSS, dextran sulfate sodium; TNBS, trinitrobenzene sulfonic acid.
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. 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. IBD patients exhibited a reduction in α-diversity and abundance of Firmicutes compared to healthy individuals. Besides, elevation in gut Proteobacteria and Bacteroidetes has been reported. 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, Sutterella, 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 gravis. In particular, elevated abundance of Pasteurellaceae, 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). UC patients exhibited a less species diversity at all stages of the disease in comparison with healthy individuals. 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. Besides, UC patients displayed even higher inflammation and dysbiosis compared to those with CD. Generally, later analysis showed that lower abundance of Akkermansia muciniphila (A. muciniphila), Butyricicoccus pullicaecorum (B. pullicaecorum), Roseburia hominis (R. hominis), and Clostridium coliun (C. coliun) and higher abundance of Fusobacterium spp. were indicated in UC patients in comparison with healthy individuals (Table 2).

Treatment with DSS resulted in a lower abundance of Bacteroidetes and Firmicutes, and a significant higher abundance of Proteobacteria. 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). 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). In addition, reduced abundance of Peptostreptococcaceae, Erysipelotrichaceae, Methylobacteriaceae, Sphingomonadaceae, and Lachnospiraceae were reported in TNBS-treated mice (Table 2). In acetic acid–induced mouse model of colitis, reductions in Clostridia, Ruminococcaceae, and Clostridiales and inductions of Enterobacteria were reported (Table 2). 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. 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). 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, Pasteurellaceae, 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. coliun, A. muciniphila, B. pullicaecorum | 118,120–122 |
| DSS   | Proteobacteria, Bacteroides, Helicobacter, Akkermansia, Desulfovibrio | 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 | Bacteroidetes, 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.\textsuperscript{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.\textsuperscript{132} Most experimental IBD models only develop in the presence of conventional microbiota, while GF mice fail to develop intestinal inflammation.\textsuperscript{133} It is agreed that constant gut dysbiosis seems to be a key factor in the aggravation of the inflammation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{99} which indicates the key causal role of commensal microbiota in the onset of IBD.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{147} while moderate inflammatory responses of DSS colitis in GF conditions were also observed.\textsuperscript{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 C1gal1 T−/−) developed spontaneous colitis with a diminished mucus layer and reduced goblet cell population, but failed to develop inflammation in GF conditions.\textsuperscript{149–151} Consistent with this, interleukin-2 (IL-2) knockout mice spontaneously developed a UC-like colitis with a 50% mortality,\textsuperscript{152} while it failed to develop inflammation when kept in GF conditions.\textsuperscript{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.\textsuperscript{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,\textsuperscript{155} while the other showed antibiotics exacerbated colitis in IL-10−/− mice by affecting the microbiota composition, Tregs population, and SCFAs production.\textsuperscript{156} Eliminating all the intestinal microbiota or not may be the interpretation for this conflicting observation as the author suggested.\textsuperscript{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.\textsuperscript{153} 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.\textsuperscript{157,158} There is
an increasing interest in SCFAs, main metabolites of gut microbiota, given its potentially important role in remission of chronic inflammation. SCFAs, including acetate, propionate, and butyrate, are produced by fermenting non-digestible and non-absorbable dietary fiber and resistant starches. SCFAs function as energy sources of colonic epithelial cells and exhibit anti-inflammatory effects by binding to G-protein-coupled receptors (GPRs). Butyrate is the most important anti-inflammatory SCFA by suppressing NF-κB and interferon-γ (IFN-γ) signaling, enhancing peroxisome proliferator-activated receptor-γ (PPAR-γ) activation, and regulating proliferation and differentiation of Tregs. 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. 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. The mucin-degrading bacteria A. muciniphila is able to produce acetate and propionate during this degradation process. 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. Correspondingly, the administration of A. muciniphila could ameliorate DSS-induced UC-type colitis in mice. Accordingly, decreased populations of SCFA-producing bacteria and SCFA production have been reported in IBD patients and colitis mice, 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 colonicocytes. In addition, literature reported that proinflammatory sulfur-reducing bacteria were more abundant in IBD patients compared to healthy individuals, which reduce sulfur and sulfur-containing compounds to hydrogen sulfide. 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, 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.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (nos. 32000082 and 31625025), Project funded by China Postdoctoral Science Foundation (2022M713405), R&D Program of Beijing Municipal Education Commission (KM202212448002), and the 111 Project (B16044).

FUNDING INFORMATION

National Natural Science Foundation of China, Grant/Award Number: nos. 32000082 and 31625025); Project funded by China Postdoctoral Science Foundation, Grant/Award Number: 2022M713405; R&D Program of Beijing Municipal Education Commission. Grant/Award Number: KM202212448002; and the 111 Project, Grant/Award Number: B16044.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

ORCID

Ning Liu https://orcid.org/0000-0002-7484-0534

REFERENCES

1. Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. Intest Res. 2018;16:26-42.
2. Park JH, Peyrin-Biroulet L, Eisenhut M, et al. IBD immunopathogenesis: A comprehensive review of inflammatory molecules. Autoimmun Rev. 2017;16:416-426.
3. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769-2778.
4. Mills S, Stamos MJ. Colonic Crohn's disease. Clin Colon Rectal Surg. 2007;20:309-313.
5. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc. 2017;92:1088-1103.
6. DeRoche TC, Xiao SY, Liu X. Histological evaluation in ulcerative colitis. Gastroenterol Rep (Oxf). 2014;2:178-192.
7. Perler BK, Ungaro R, Baird G, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC Gastroenterol. 2019;19:47.
8. Si X, Liu N, Jia H, et al. Gut relief formula attenuates dextran sulfate sodium-induced colitis by regulating NF-kappaB signaling and the intestinal microbiota in mice. Food Funct. 2021;12:10983-10993.
9. Collaborators GBDIBD. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5:17-30.
10. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12:720-727.
11. Caruso R, Lo BC, Núñez G. Host-microbiota interactions in inflammatory bowel disease. Nat Rev Immunol. 2020;20:411-426.
12. Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res. 2019;2019:7247238.
13. Rogler G, Vavricka S. Exposome in IBD: recent insights in environmental factors that influence the onset and course of IBD. Inflamm Bowel Dis. 2015;21:400-404.
14. Zhang Y-Z, Li Y-Y. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014;20:91-99.
15. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47:979-986.
16. McGovern DP, Kugathasan S, Cho JH. Genetics of inflammatory bowel diseases. Gastroenterology. 2015;149:1163-1176.e2.
17. Llewellyn SR, Britton GJ, Contijoch EJ, et al. Interactions between diet and the intestinal microbiota alter intestinal permeability and colitis severity in mice. Gastroenterology. 2018;154:1037-1046.e2.
18. Zhai Z, Zhang F, Cao R, et al. Cecropin A alleviates inflammation through modulating the gut microbiota of C57BL/6 mice with DSS-induced IBD. Front Microbiol. 2019;10:1595.
19. Yadav V, Varuhum F, Bravo R, et al. Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets. Transl Res. 2016;176:38-68.
20. Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annu Rev Immunol. 2012;30:759-795.
21. Li Z, Zhu H, Zhang L, et al. The intestinal microbiome and Alzheimer's disease: A review. Animal Model Exp Med. 2018;1:180-188.
22. Mukherjee PK, Sendib D, Hoarau G, et al. Mycobacteria in gastrointestinal diseases. Nat Rev Gastroenterol Hepatol. 2015;12:77-87.
23. Forbes JD, Bernstein CN, Tremlett H, et al. A fungal world: could the gut mycobacteria be involved in neurological disease? Front Microbiol. 2018;9:3249.
24. Santus W, Devlin JR, Behnjen S. Crossing Kingdoms: how the mycobacteria and fungal-bacterial interactions impact host health and disease. Infect Immun. 2021;89:e00648-20.
25. Panpetch W, Hengrach P, Nilglate S, et al. Additional Candida albicans administration enhances the severity of dextran sulfate solution induced colitis mouse model through leaky gut-enhanced systemic inflammation and gut-dysbiosis but attenuated by Lactobacillus rhamnosus L34. Gut Microbes. 2020;11:465-480.
26. Richard ML, Sokol H. The gut mycobacteria: insights into analysis, environmental interactions and role in gastrointestinal diseases. Nat Rev Gastroenterol Hepatol. 2019;16:331-345.
27. Ungaro F, Massimino L, Furfaro F, et al. Metagenomic analysis of intestinal mucosa revealed a specific eukaryotic gut virome signature in early-diagnosed inflammatory bowel disease. Gut Microbes. 2019;10:149-158.
28. Adilighdam F, Amatullah H, Digumarthi S, et al. Human enteric viruses autonomously shape inflammatory bowel disease phenotype through divergent innate immunomodulation. Sci Immunol. 2022;7:eabn6660.
29. Norman JM, Handley SA, Baldridge MT, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell. 2015;160:447-460.
30. Wang Z, Guo K, Liu Y, et al. Dynamic impact of virome on colitis and colorectal cancer: Immunity, inflammation, prevention and treatment. Semin Cancer Biol. 2021.
31. Clooney AG, Sutton TDS, Shkopoivan AN, et al. Whole-virome analysis sheds light on viral dark matter in inflammatory bowel disease. Cell Host Microbe. 2019;26:764-778.e5.
32. Liu S, Zhao W, Lan P, et al. The microbiome in inflammatory bowel diseases: from pathogenesis to therapy. Protein Cell. 2021;12:331-345.
33. Zuo T, Ng SC. The gut microbiota in the pathogenesis and therapeutic strategies of inflammatory bowel disease. Front Microbiol. 2018;9:2247.
34. Zhang M, Sun K, Wu Y, et al. Interactions between intestinal microbiota and host immune response in inflammatory bowel disease. Front Immunol. 2017;8:942.
35. Cahana I, Iraqui FA. Impact of host genetics on gut microbiome: Take-home lessons from human and mouse studies. Animal Model Exp Med. 2020;3:229-236.
36. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464:59-65.
37. Human Microbiome Project C. Structure function and diversity of the healthy human microbiome. Nature. 2012;486:207-214.
38. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. Nature. 2011;473:174-180.
39. Koenig JE, Spor A, Scalfone N, et al. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci USA. 2011;108(Suppl 1):4578-4585.
40. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17:690-703.
41. Sommer F, Bäckhed F. The gut microbiota—masters of host development and physiology. Nat Rev Microbiol. 2013;11:227-238.
42. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature. 2009;457:480-484.
43. Nishida A, Inoue R, Inatomi O, et al. Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol. 2018;11:1-10.
44. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. Proc Nutr Soc. 2003;62:67-72.
45. Sartor RB. Microbial influences in inflammatory bowel diseases. Gastroenterology. 2008;134:577-594.
46. Cantarel BL, Lombard V, Henrisat B. Complex carbohydrate utilization by the healthy human microbiome. PLoS One. 2012;7:e28742.
47. Mattjissen F, Alex S, Swarts HJ, et al. Angptl4 serves as an endogenous inhibitor of intestinal lipid digestion. Mol Metab. 2014;3:135-144.
48. Korecka A, de Wouters T, Cultrone A, et al. ANGPTL4 expression induced by butyrate and resiglitazone in human intestinal epithelial cells utilizes independent pathways. Am J Physiol Gastrointest Liver Physiol. 2013;304:G1025-G1037.
49. Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. World J Gastroenterol. 2015;21:8787-8803.
50. LeBlanc JG, Laiño JE, del Valle MJ, et al. B-group vitamin production by lactic acid bacteria—current knowledge and potential applications. J Appl Microbiol. 2011;111:1297-1309.
51. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009;9:313-323.
52. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020;30:492-506.
53. Hafelfmeier S, Lawson MA, Slack E, et al. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. Science. 2010;328:1705-1709.
54. Gomez de Agüiero M, Galán-Vonarburg SC, Fuhrer T, et al. Animal models of inflammatory bowel disease. J Biomed Biotechnol. 2013;7:1341-1357.
55. Elson CO, Beagley KW, Sharmanov AT, et al. Hapten-induced model of murine inflammatory bowel disease: mucosa immune responses and protection by tolerance. J Immunol. 1996;157:2174-2185.
56. Motavalli-Naeini A, Andalib S, Rabbani M, et al. Validation and optimization of experimental colitis induction in rats using 2, 4, 6-trinitrobenzene sulfonic acid. Res Pharmaceut Sci. 2012;7:159-169.
57. Kawada M, Arihiro A, Mizoguchi E. Insights from advances in research of chemically induced experimental models of human inflammatory bowel disease. World J Gastroenterol. 2007;13:5581-5593.
58. Wang YH, Ge B, Yang XL, et al. Proanthocyanidins from grape seeds modulates the nuclear factor-kappa B signal transduction pathways in rats with TNBS-induced recurrent ulcerative colitis. Int Immunopharmacol. 2011;11:1620-1627.
59. Liu Y, Wang X, Hu CA. Therapeutic potential of amino acids in inflammatory bowel disease. Nutrients. 2017;9:920.
60. Pandiyan P, Bhaskaran N, Zou M, et al. Microbiome dependent regulation of T(regs) and Th17 cells in mucosa. Front Immunol. 2019;10:426.
61. Khan R, Petersen FC, Shekhar S. Commensal bacteria: an emerging player in defense against respiratory pathogens. Front Immunol. 2019;10:1203.
62. Fabich AJ, Jones SA, Chowdhury FZ, et al. Comparison of carbon nutrition for pathogenic and commensal Escherichia coli strains in the mouse intestine. Infect Immun. 2008;76:1143-1152.
63. Momose Y, Hirayama K, Itoch K. Competition for proline between CD4 T cells in the colonic lamina propria under normal and inflammatory conditions. J Immunol. 2008;180:559-568.
64. Pandiyan P, Bhaskaran N, Zou M, et al. Microbiome dependent regulation of T(regs) and Th17 cells in mucosa. Front Immunol. 2019;10:426.
65. Khan R, Petersen FC, Shekhar S. Commensal bacteria: an emerging player in defense against respiratory pathogens. Front Immunol. 2019;10:1203.
66. Fabich AJ, Jones SA, Chowdhury FZ, et al. Comparison of carbon nutrition for pathogenic and commensal Escherichia coli strains in the mouse intestine. Infect Immun. 2008;76:1143-1152.
67. Momose Y, Hirayama K, Itoch K. Competition for proline between indigenous Escherichia coli and E. coli O157:H7 in gnotobiotic mice associated with infant intestinal microbiota and its contribution to the colonization resistance against E. coli O157:H7. Antonie Van Leeuwenhoek. 2008;94:165-171.
68. Matitya R, Leatham-Jensen MP, Gibson T, et al. Nutritional basis for colonization resistance by human commensal Escherichia coli strains HS and Nissle 1917 against pathogenic Escherichia coli O157:H7. Mol Nutr Food Res. 2010;54:1673-1680.
69. Cotter PD, Ross RP, Hill C. Bacteriocin—a viable alternative to antibiotics? Nat Rev Microbiol. 2013;11:95-105.
70. Rea MC, Sit CS, Clayton E, et al. Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against Clostridium difficile. Proc Natl Acad Sci USA. 2010;107:9352-9357.
71. Perše M, Cesar A. Dextran sodium sulphate colitis mouse model: traps and tricks. J Biomed Biotechnol. 2012;2012:718617.
72. Wirtz S, Popp V, Kindermann M, et al. Chemically induced mouse colitis and their application in drug research. Drug Des Devel Ther. 2013;7:1341-1357.
73. Elson CO, Beagley KW, Sharmanov AT, et al. Hapten-induced model of murine inflammatory bowel disease: mucosa immune responses and protection by tolerance. J Immunol. 1996;157:2174-2185.
74. Motavalli-Naeini A, Andalib S, Rabbani M, et al. Validation and optimization of experimental colitis induction in rats using 2, 4, 6-trinitrobenzene sulfonic acid. Res Pharmaceut Sci. 2012;7:159-169.
75. Kawada M, Arihiro A, Mizoguchi E. Insights from advances in research of chemically induced experimental models of human inflammatory bowel disease. World J Gastroenterol. 2007;13:5581-5593.
76. Wang YH, Ge B, Yang XL, et al. Proanthocyanidins from grape seeds modulates the nuclear factor-kappa B signal transduction pathways in rats with TNBS-induced recurrent ulcerative colitis. Int Immunopharmacol. 2011;11:1620-1627.
77. Liu Y, Wang X, Hu CA. Therapeutic potential of amino acids in inflammatory bowel disease. Nutrients. 2017;9:920.
78. Randhawa PK, Singh K, Singh N, et al. A review on chemical-induced inflammatory bowel disease models in rodents. Korean J Physiol Pharmacol. 2014;18:279-288.
79. Niu X, Fan T, Li W, et al. Protective effect of sanguinarine against acetic acid-induced ulcerative colitis in mice. Toxicol Appl Pharmacol. 2013;267:256-265.
80. Hwang JH, Kim TH, Kim YH, et al. Gadd45β promotes regeneratiion after injury through TGFβ-dependent restitution in experimental colitis. Exp Mol Med. 2019;51:1-14.
81. Wales AD, Woodward MJ, Pearson GR. Attaching-effacing bacteria in animals. J Comp Pathol. 2005;132:1-26.
82. Silberger DJ, Zindl CL, Weaver CT. Citrobacter rodentium: a model enteropathogen for understanding the interplay of innate and adaptive components of type 3 immunity. Mucosal Immunol. 2017;10:1108-1117.
83. Collins JW, Keeney KM, Crepin VF, et al. Citrobacter rodentium: infection, inflammation and the microbiota. Nat Rev Microbiol. 2014;12:612-623.
84. Bhinder G, Sham HP, Chan JM, et al. The Citrobacter rodentium mouse model: studying pathogen and host contributions to infectious colitis. J Vis Exp. 2013;72:e50222.
85. Nell S, Suerbaum S, Josenhans C. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models. Nat Rev Microbiol. 2010;8:564-577.
86. Petty NK, Bulgirin R, Crepin VF, et al. The Citrobacter rodentium genome sequence reveals convergent evolution with human pathogenic Escherichia coli. J Bacteriol. 2010;192:525-538.
87. Borenshtein D, McBee ME, Schauer DB. Utility of the Citrobacter rodentium infection model in laboratory mice. Curr Opin Gastroenterol. 2008;24:32-37.
88. Borenshtein D, Nambar PR, Groff EB, et al. Development of fatal colitis in FVB mice infected with Citrobacter rodentium. Infect Immun. 2007;75:3271-3281.
89. Goyal N, Rana A, Ahlawat A, et al. Animal models of inflammatory bowel disease: a review. Inflammopharmacology. 2014;22:219-233.
90. Zhang Y, Ji J, Lin Y, et al. Glucose attenuates citrobacter rodentium-induced colitis by regulating ATF6-mediated endoplasmic reticulum stress in mice. Mol Nutr Food Res. 2021;65:e2001065.
91. Hou YC, Wu JM, Wang MY, et al. Glutamine supplementation attenuates expressions of adhesion molecules and chemokine receptors on T cells in a murine model of acute colitis. Mediators Inflamm. 2014;2014:837107.
92. Chu CC, Hou YC, Pai MH, et al. Pretreatment with alanyl-glutamine suppresses T-helper-cell-associated cytokine expression and reduces inflammatory responses in mice with acute DSS-induced colitis. J Nutr Biochem. 2012;23:1092-1099.
93. Nunes NS, Chandran P, Sündy M, et al. Therapeutic ultrasound attenuates DSS-induced colitis through the cholinergic anti-inflammatory pathway. EBioMedicine. 2019;45:495-510.
94. Liu B, Liu T, Wang X, et al. Effects of Guchang capsule on dextran sulphate sodium-induced experimental ulcerative colitis in mice. Evid Based Complement Alternat Med. 2016;2016:3150651.

95. Jin B-R, Chung K-S, Cheon S-Y, et al. Rosmarinic acid suppresses colonic inflammation in dextran sulphate sodium (DSS)-induced mice via dual inhibition of NF-κB and STAT3 activation. Sci Rep. 2017;7:46252.

96. Creyns B, Cremer J, Hoshino T, et al. Fibrogenesis in chronic DSS colitis is not influenced by neutralisation of regulatory T cells, of major T helper cytokines or absence of IL-13. Sci Rep. 2019;9:10064.

97. Ben-Ami Shor D, Lachnish J, Bashi T, et al. Immunomodulation of murine chronic DSS-induced colitis by tufts-in-phosphorylcholine. J Clin Med. 2019;9:65.

98. Vidal-Lletjós S, Andriamihaja M, Blais A, et al. Mucosal healing progression after acute colitis in mice. World J Gastroenterol. 2019;25:3572-3589.

99. Abad C, Martinez C, Juarranz MG, et al. Therapeutic effects of vasoactive intestinal peptide in the trinitrobenzene sulfoxonic acid mice model of Crohn's disease. Gastroenterology. 2003;124:961-971.

100. Fuss U, Boivivant M, Lacy B, et al. The interrelated roles of TGF-beta and IL-10 in the regulation of experimental colitis. J Immunol. 2002;168:900-908.

101. Lee IA, Hyun YJ, Kim DH. Berberine ameliorates TNBS-induced colitis by inhibiting lipid peroxidation, enterobacterial growth and NF-κB activation. Eur J Pharmacol. 2010;648:162-170.

102. Oh SY, Cho KA, Kang JL, et al. Comparison of experimental mouse models of inflammatory bowel disease. Int J Mol Med. 2014;33:333-340.

103. Colombo BB, Fattori V, Guazelli CF, et al. Vinpocetine ameliorates acetic acid-induced colitis by inhibiting NF-κB activation in mice. Inflammation. 2018;41:1276-1289.

104. Zhang J, Jiao Y, Hou S, et al. S100A4 contributes to colitis development by increasing the adherence of Citrobacter rodentium in intestinal epithelial cells. Sci Rep. 2017;7:12099.

105. Tsai PY, Zhang B, He WQ, et al. IL-22 upregulates epithelial claudin-2 to drive diarrhea and enteric pathogen clearance. Cell Host Microbe. 2017;21:671-681.e4.

106. Park JI, Seo SM, Park JH, et al. A murine colitis model developed using a combination of dextran sulfate sodium and Citrobacter rodentium. J Microbiol. 2018;56:272-279.

107. Durgan DJ, Lee J, McCullough LD, et al. Examining the role of the microbiota-gut-brain axis in stroke. Stroke 2019;50:2270-2277.

108. Fava F, Danese S. Intestinal microbiota in inflammatory bowel disease: friend of foe? World J Gastroenterol. 2011;17:557-566.

109. Dovroils N, Michalopoulos G, Theodoropoulos GE, et al. The interplay between mucosal microbiota composition and host gene-expression is linked with infliximab response in inflammatory bowel diseases. Microorganisms. 2020;8:438.

110. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. Semin Immunopathol. 2015;37:47-55.

111. Frank DN, St Amand AL, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA. 2007;104:13780-13785.

112. Walker AW, Sanderson JD, Churcher C, et al. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. BMC Microbiol. 2011;11:7.

113. Sartor RB, Wu GD. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology. 2017;152:327-339.e4.

114. Knox NC, Forbes JD, Peterson CL, et al. The gut microbiome in inflammatory bowel disease: lessons learned from other immune-mediated inflammatory diseases. Am J Gastroenterol. 2019;114:1051-1070.

115. Gevers D, Kugathasan S, Denson LA, et al. The treatment-naive microbiome in new-onset Crohn’s disease. Cell Host Microbe. 2014;15:382-392.

116. Bartels LE, Jepsen P, Christensen LA, et al. Diagnosis of helicobacter pylori infection is associated with lower prevalence and subsequent incidence of Crohn’s disease. J Crohns Colitis. 2016;10:443-448.

117. Mirsepasi-Lauridsen HC, Vrankx K, Engberg J, et al. Disease-specific enteric microbiome dysbiosis in inflammatory bowel disease. Front Med. 2018;5:304.

118. Vester-Andersen MK, Mirsepasi-Lauridsen HC, Prosberg MV, et al. Increased abundance of proteobacteria in aggressive Crohn’s disease seven years after diagnosis. Sci Rep. 2019;9:13473.

119. Shaw KA, Bertha M, Hofmekler T, et al. Dysbiosis, inflammation, and response to treatment: a longitudinal study of pediatric subjects with newly diagnosed inflammatory bowel disease. Genome Med. 2016;8:75.

120. Bajer L, Kverka M, Kostovic M, et al. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. World J Gastroenterol. 2017;23:4548-4558.

121. Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut. 2014;63:1275-1283.

122. Okusa T, Sato N, Ogihara T, et al. Fusobacterium varium localized in the colonic mucosa of patients with ulcerative colitis stimulates species-specific antibody. J Gastroenterol Hepatol. 2002;17:849-853.

123. Li AL, Ni WW, Zhang QM, et al. Effect of cinnamon essential oil on gut microbiota in the mouse model of dextran sodium sulfate-induced colitis. Microbiol Immunol. 2020;64:23-32.

124. Häkkanson Å, Tormo-Badia N, Baridi A, et al. Immunological alteration and changes of gut microbiota after dextran sulfate sodium (DSS) administration in mice. Clin Exp Med. 2015;15:107-120.

125. Jang SE, Jeong JJ, Kim JK, et al. Simultaneous amelioration of colitis and liver injury in mice by bifidobacterium longum LC67 and Lactobacillus plantarum LC27. Sci Rep. 2018;8:7500.

126. Jang SE, Lim SM, Jeong JJ, et al. Gastrointestinal inflammation by gut microbiota disturbance induces memory impairment in mice. Mucosal Immunol. 2018;11:369-379.

127. Li P, Lei J, Hu G, et al. Matrine mediates inflammatory response via gut microbiota in TNBS-induced murine colitis. Front Physiol. 2019;10:28.

128. Wu X, Zheng Y, Ma J, et al. The effects of dietary glycine on the acetic acid-induced mouse model of colitis. Mediators Inflamm. 2020;2020:5867627.

129. K-da S, Peerakietkhajorn S, Siringoringo B, et al. Oligosaccharides from Gracilaria fisheri ameliorate gastrointestinal dysmotility and other symptoms of rodent ulcerative colitis. Cell Physiol Biochem. 2016;2016:3150651.
135. DeGruttola AK, Low D, Mizoguchi A, et al. Current understanding of dysbiosis in disease in human and animal models. Inflamm Bowel Dis. 2016;22:1137-1150.

136. Strauss J, Kaplan GG, Beck PL, et al. Invasive potential of gut mucosa-derived Fusobacterium nucleatum positively correlates with IBD status of the host. Inflamm Bowel Dis. 2011;17:1971-1978.

137. Okusa T, Yoshida T, Sato N, et al. Commensal bacteria can enter colonic epithelial cells and induce proinflammatory cytokine secretion: a possible pathogenic mechanism of ulcerative colitis. J Med Microbiol. 2009;58:535-545.

138. Du Z, Hudcovic T, Mrazek J, et al. Development of gut inflammation in mice colonized with mucosa-associated bacteria from patients with ulcerative colitis. Gut pathogens. 2015;7:32.

139. Natividad JM, Pinto-Sanchez MI, Galipeau HJ, et al. Ecotherapy rich in fircmium decreases susceptibility to colitis in a humanized gnotobiotic mouse model. Inflamm Bowel Dis. 2015;21:1883-1893.

140. Gupta S, Allen-Vercroe E, Petrof EO. Fecal microbiota transplantation: in perspective. Therap Adv Gastroenterol. 2016;9:229-239.

141. Kho ZY, Lal SK. The human gut microbiome—a potential controller of wellness and disease. Front Microbiol. 2018;9:1835.

142. Khan I, Ullah N, Zha L, et al. Alteration of gut microbiota in inflammatory bowel disease (IBD): cause or consequence? IBD treatment targeting the gut microbiome. Pathogens. 2019;8:126.

143. Hyun CK. Molecular and pathophysiological links between metabolic disorders and inflammatory bowel diseases. Int J Mol Sci. 2021;22:9139.

144. Kitajima S, Morimoto M, Sagara E, et al. Dextran sodium sulfate-induced colitis in germ-free IqJic mice. Exp Anim. 2001;50:387-395.

145. Hernández-Chirlaque C, Aranda CJ, Ocon B, et al. Germ-free and antibiotic-treated mice are highly susceptible to epithelial injury in DSS colitis. J Crohns Colitis. 2016;10:1324-1335.

146. Ward NL, Phillips CD, Nguyen DD, et al. Antibiotic treatment induces long-lasting changes in the fecal microbiota that protect against colitis. Inflammat Mat Bowel Dis. 2016;22:2328-2340.

147. Bylund-Fellenius AC, Landström E, Axelsson LG, et al. Experimental colitis induced by dextran sulphate in normal and germfree mice. Microbial Ecol Health Dis. 1994;7:207-215.

148. Hudcovic T, Štěpánková R, Cebra J, et al. The role of microflora in the development of intestinal inflammation: acute and chronic colitis induced by dextran sulphate in germ-free and conventional mice. Inflamm Bowel Dis. 2009;15:653-660.

149. Perez-Muñoz ME, Bergstrom K, Peng V, et al. Discordance between changes in the gut microbiota and pathogenicity in a mouse model of spontaneous colitis. Gut Microbes. 2014;5:286-295.

150. Van der Sluis M, De Koning BA, De Bruijin AC, et al. Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. Gastroenterology. 2006;131:117-129.

151. Bergstrom K, Fu J, Johansson ME, et al. Core 1- and 3-derived O-glycans collectively maintain the colonic mucus barrier and protect against spontaneous colitis in mice. Mucosal Immunol. 2017;10:91-103.

152. Sadlack B, Merz H, Schorle H, et al. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. Cell. 1993;75:253-261.

153. Contractor NV, Bassiri H, Reya T, et al. Lymphoid hyperplasia, autoimmunity, and compromised intestinal intraepithelial lymphocyte development in colitis-free gnotobiotic IL-2-deficient mice. J Immunol. 1998;160:385-394.

154. Sellon RK, Tonkonogy S, Schultz M, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. Infect Immun. 1998;66:5224-5231.

155. Madsen KL, Doyle JS, Tavernini MM, et al. Antibiotic therapy ameliorates colitis in interleukin 10 gene-deficient mice. Gastroenterology. 2000;118:1094-1105.

156. Shen B, Hu J, Song H, et al. Antibiotics exacerbated colitis by affecting the microbiota, Treß cells and SCFAs in IL10-deficient mice. Biomed Pharmacother. 2019;114:108849.

157. Montenegro-Burke JR, Kok BP, Guijas C, et al. Metabolomics activity screening of T cell-induced colitis reveals anti-inflammatory metabolites. Sci Signal. 2021;14:eabf6584.

158. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020;17:223-237.

159. Deleu S, Machiels K, Raes J, et al. Short chain fatty acids and its producing organisms: An overlooked therapy for IBD? EBioMedicine. 2021;66:103293.

160. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277.

161. Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019;16:461-478.

162. Donohoe DR, Garge N, Zhang X, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. 2011;13:517-526.

163. Torbourn AN, Macia L, Mackay CR. Diet, metabolites, and “western-style” inflammatory diseases. Immunity. 2014;40:833-842.

164. Lührs H, Gerke T, Müller JG, et al. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol. 2002;37:458-466.

165. Klampfer L, Huang J, Sasazuki T, et al. Inhibition of interferon gamma signaling by the short chain fatty acid butyrate. Mol Cancer Res. 2003;1:855-862.

166. Kinoshita M, Suzuki Y, Saito Y. Butyrate reduces colonic paracellular permeability by enhancing PPARgamma activation. Biochem Biophys Res Commun. 2002;293:827-831.

167. Kespohl M, Vachharajani N, Loo M, et al. The microbial metabolite butyrate induces expression of Thy1-associated factors in CD4(+) T cells. Front Immunol. 2017;8:1036.

168. Willing B, Halfvarson J, Dicksved J, et al. Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal Crohn's disease. Inflamm Bowel Dis. 2009;15:653-660.

169. Varela E, Manichanh C, Gallart M, et al. Colonisation by Faecalibacterium prausnitzii and maintenance of clinical remission in patients with ulcerative colitis. Aliment Pharmacol Ther. 2013;38:151-161.

170. Rajca S, Grondin V, Louis E, et al. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn’s disease. Inflamm Bowel Dis. 2014;20:978-986.

171. Van Herreweghen F, Van den Abbeele P, De Mulder T, et al. Gut pathogens affecting the microbiota, Treg cells and SCFAs in IL10-deficient mouse. EBioMedicine. 2021;10:2259.

172. Wu Z, Huang S, Li T, et al. Gut microbiota from green tea polyphenol-dosed mice improves intestinal epithelial homeostasis and ameliorates experimental colitis. Microbiome. 2021;9:184.

173. Bian X, Wu W, Yang L, et al. Administration of akkermansia muciniphila ameliorates dextran sulfate sodium-induced ulcerative colitis in mice. Front Microbiol. 2019;10:2259.

174. Wang W, Chen L, Zhou R, et al. Increased proportions of Faecalibacterium prausnitzii and maintenance of clinical remission in patients with ileal Crohn's disease. Inflamm Bowel Dis. 2013;38:151-161.

175. Smith FM, Coffey JC, Kell MR, et al. A characterization of anaerobic colonization and associated mucosal adaptations in the diseased ileal pouch. Colorectal Dis. 2005;7:563-570.
177. Verma R, Verma AK, Ahuja V, et al. Real-time analysis of mucosal flora in patients with inflammatory bowel disease in India. *J Clin Microbiol*. 2010;48:4279-4282.

178. Scanlan PD, Shanahan F, Marchesi JR. Culture-independent analysis of desulfovibrions in the human distal colon of healthy, colorectal cancer and polypectomized individuals. *FEMS Microbiol Ecol*. 2009;69:213-221.

179. Ohkusa T, Okayasu I, Ogihara T, et al. Induction of experimental ulcerative colitis by *Fusobacterium varium* isolated from colonic mucosa of patients with ulcerative colitis. *Gut*. 2003;52:79-83.

How to cite this article: Zhang Y, Si X, Yang L, Wang H, Sun Y, Liu N. Association between intestinal microbiota and inflammatory bowel disease. *Anim Models Exp Med*. 2022;5:311-322. doi: 10.1002/ame2.12255