REVIEW

# Dietary Patterns and Gut Microbiota: The Crucial Actors in Inflammatory Bowel Disease

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## ABSTRACT

It is widely believed that diet and the gut microbiota are strongly related to the occurrence and progression of inflammatory bowel disease (IBD), but the effects of the interaction between dietary patterns and the gut microbiota on IBD have not been well elucidated. In this article, we aim to explore the complex relation between dietary patterns, gut microbiota, and IBD. We first comprehensively summarized the dietary patterns associated with IBD and found that dietary patterns can modulate the occurrence and progression of IBD through various signaling pathways, including mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPKs), signal transducer and activator of transcription 3 (STAT3), and NF-$\kappa$B. Besides, the gut microbiota performs a vital role in the progression of IBD, which can affect the expression of IBD susceptibility genes, such as dual oxidase 2 (*DUOX2*) and *APOA-1* , the intestinal barrier (in particular, the expression of tight junction proteins), immune function (especially the homeostasis between effector and regulatory T cells) and the physiological metabolism, in particular, SCFAs, bile acids (BAs), and tryptophan metabolism. Finally, we reviewed the current knowledge on the interaction between dietary patterns and the gut microbiota in IBD and found that dietary patterns modulate the onset and progression of IBD, which is partly attributed to the regulation of the gut microbiota (especially SCFAs-producing bacteria and *Escherichia coli*). *Faecalibacteria* as "microbiomarkers" of IBD could be used as a target for dietary interventions to alleviate IBD. A comprehensive understanding of the interplay between dietary intake, gut microbiota, and IBD will facilitate the development of personalized dietary strategies based on the regulation of the gut microbiota in IBD and expedite the era of precision nutritional interventions for IBD. *Adv Nutr* 2022;13:1628–1651.

**Statement of Significance:** Diet and the gut microbiota are strongly related to the occurrence and progression of inflammatory bowel disease. A complete understanding of the crosstalk between dietary patterns, the gut microbiota, and inflammatory bowel disease will facilitate the development of personalized dietary strategies based on regulation of the gut microbiota in inflammatory bowel disease.

Keywords: dietary patterns, gut microbiota, short chain fatty acids, bile acids, tryptophan, inflammatory bowel disease, dysbacteriosis

## Introduction

Inflammatory bowel disease (IBD), which mainly comprises ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing, and relieved inflammatory intestinal disorder, characterized by abdominal pain, diarrhea, and weight loss (1, 2). IBD has evolved into a global disease with increasing prevalence in every continent, especially North America (>2 million) and Europe (>3.2 million) (3). The global prevalence of IBD was >0.3% at the beginning of the 21st century, and 57% of the 6.8 million cases of IBD in 2017 occurred in female subjects (4, 5). The precise pathogenesis of IBD remains unclear, but the most accepted hypothesis is that environmental factors trigger an abnormal immune response against the gut microbiota in genetically susceptible hosts (6). Various environmental factors could affect intestinal microbial homeostasis, which is associated with human health (7). Diet, as one of the environmental factors, is widely considered to play a crucial role in the development of IBD (8).

Numerous studies have shown that dietary patterns, including the Western diet (WD) (9, 10), the Mediterranean diet (MED) (11), the semi-vegetarian diet (SVD) (12), the IBD anti-inflammatory diet (IBD-AID) (13), the specific carbohydrate diet (SCD) (14), the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet (Low FODMAP diet) (15), the gluten-free diet (GFD) (16), etc.,



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have significant effects on the development of IBD. Although the exact mechanisms by which dietary interventions affect IBD remain unclear, some plausible explanations have been proposed. First, the diet may modulate mucosal barrier function, which is a critical factor in the pathogenesis of IBD (17). Second, the diet may be involved in the inflammatory response and immune function (18, 19). Third, the diet may contribute to shaping the gut microbiota and its metabolites (20). A growing body of evidence suggests that the effects of dietary patterns on IBD may be attributable to the alteration of the gut microbiota (17, 21, 22) and gut microbiota-derived metabolites (23), because the gut microbiota acts as an effector between the diet and IBD, and bacterial flagellin serves as an antigen to modulate the host immune response (22, 24).

Most studies of diets, the gut microbiota, and IBD have mainly focused on their interrelations, for instance, diet and IBD (1, 25–28), or the gut microbiota and IBD (2, 29–32), but few studies have regarded all 3 factors as a whole. Considering that diet may affect immune homeostasis via the gut microbiota in individuals with a genetic susceptibility to IBD, a complete understanding of the crosstalk between diet, the gut microbiota, and IBD would have great significance for the prevention and/or treatment of IBD. Therefore, this review first summarizes the relations between various dietary patterns and IBD, and we further present the underlying mechanisms. Alterations of the gut microbiota and its function in IBD patients are then discussed, and the mechanisms by which the gut microbiota contributes to IBD are further proposed. Finally, the interactions between dietary patterns and the gut microbiota that underlie the occurrence and development of IBD are highlighted. The aim of this article is to summarize the complex relations among dietary patterns, the gut microbiota, and IBD to facilitate the formulation of personalized dietary strategies based on individual gut microbiota characteristics and to expedite the era of precision nutritional interventions for IBD.

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Abbreviations used: Ah, aryl-hydrocarbon receptor; AIEC, adherent-invasive *Escherichia coli*; BAs, bile acids; CD, Crohn's disease; CDED, Crohn's disease exclusion diet; CRP, C-reactive protein; DSS, dextran sodium sulfate; *DUOX2*, dual oxidase 2; *E. coli*, *Escherichia coli*; EEN, exclusive enteral nutrition; EVOO, extra virgin olive oil; FMD, fasting-mimicking diet; GFD, gluten-free diet; GPCR, G-protein coupled receptor; HDAC, histone deacetylase; HSD, high-salt diet; IBD, inflammatory bowel disease; IBD-AID, IBD anti-inflammatory diet; IBS, irritable bowel syndrome; ICD, ileum Crohn's disease; IEC, intestinal epithelial cell; IF, intermittent fasting; KD, ketogenic diet; low FODMAP diet, low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet; MAPK, mitogen-activated protein kinase; MED, Mediterranean diet; mTOR, mammalian target of rapamycin; Muc2, mucin 2; NLRP3, NOD-, LRR-, and pyrin domain-containing 3; NLR, Nod-like receptor; PAMPs, pathogen-associated molecular patterns; PD, paleolithic diet; PEN, partial enteral nutrition; PPAR-$\gamma$, peroxisome proliferator-activated receptor $\gamma$; ROR$\gamma$t, retinoid-related orphan nuclear receptor-$\gamma$t; ROS, reactive oxygen species; SCD, specific carbohydrate diet; SGK1, serum glucocorticoid kinase 1; STAT3, signal transducer and activator of transcription 3; SVD, semivegetarian diet; T cell, T lymphocyte cell; TLR, Toll-like receptor; Treg cells, regulatory T cells; UC, ulcerative colitis; VD, vegetarian diet; VDR, vitamin D receptor; WD, Western diet.

## Dietary Patterns and IBD

### WD

The WD features a high intake of red and processed meat, high-fat dairy products, high-sugar drinks, refined grains, butter, etc., and a low intake of dietary fiber, which has been considered a possible cause of the increased incidence of IBD (4, 5, 10, 33, 34). A large ($n = 366{,}351$) European prospective cohort study found a positive correlation between the intake of sugar and soft drinks and the risk of UC ($P_{trend} = 0.02$) (35). A cross-sectional study among adults with and without IBD in the USA found that adopting a healthy well-balanced diet (especially limiting added sugars) may be beneficial to the overall health of women with IBD (36). Similarly, a systematic review (including 2609 IBD patients and over 4000 controls) indicated that a high intake of total fat, PUFAs, and meat is positively associated with the risk of UC and CD. Conversely, high vegetables or fiber and fruit consumption could decrease the risk of UC and CD, respectively (10), which indicates that the pathogenesis of IBD may be related to a variety of dietary factors. However, another study demonstrated that controlling the consumption of red and processed meat in patients with CD in remission does not reduce the incidence of disease (time to any ($P = 0.61$) or moderate/severe ($P = 0.50$) relapse) (37). Interestingly, a recent study showed that a WD significantly aggravated dextran sodium sulfate (DSS)-induced experimental colitis in BALB/c mice, but switching to a healthy diet reduced colon inflammation (38). A recent Dutch cohort study with 2-y longitudinal clinical follow-up found that a dietary pattern considered to be a "Western" pattern was associated with the exacerbation of IBD (39). Subsequently, they conducted another large prospective population-based cohort, which further found that Western dietary patterns and carnivorous patterns were associated with the development of CD and UC, respectively (40).

A WD could inhibit the expression of mucin 2 (Muc2), the first line of defense against microbial invasion in the intestine, thereby increasing the permeability of the epithelial barrier (41). In addition, a WD may upregulate the concentrations of Toll-like receptors (TLRs), such as TLR2 and TLR4, which are also significantly elevated in patients with IBD (42, 43). A recent study revealed that activation of the mammalian target of rapamycin (mTOR) is the basis of the intestinal dysfunction and inflammation caused by a WD (44), and that the excessive inflammatory responses further disrupt the balance of intestinal T helper 17 (Th17) and regulatory T (Treg) cells, ultimately increasing the risk of IBD (25, 45), as shown in **Figure 1**.

Protein, fat, and sugar have been widely studied as the main ingredients of a WD. A recent case-control study indicated that a high-protein dietary pattern is positively related to the risk of IBD, whereas a high-vegetable dietary pattern may reduce IBD risk (46). Previous studies have demonstrated that high glucose intake can increase the permeability of the gut barrier and the sensitivity of proinflammatory cytokines, and that it can activate transforming growth

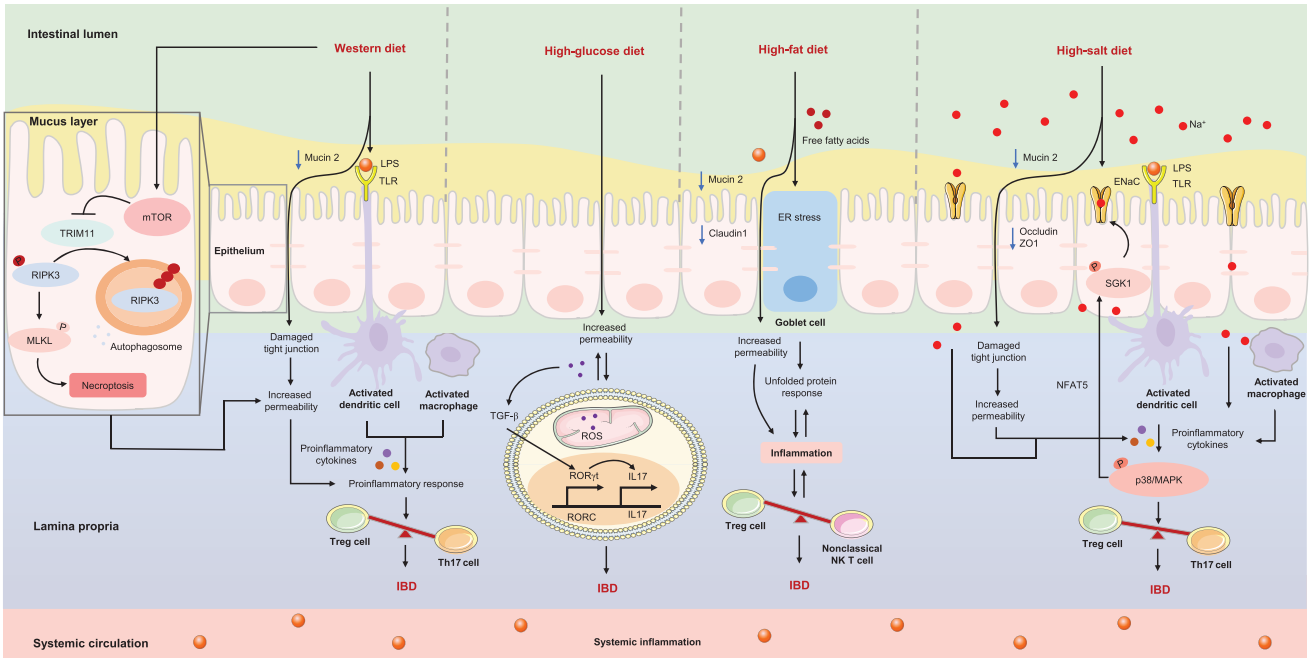


**FIGURE 1** Potential mechanisms of proinflammatory diets on IBD. The Western diet not only increases the permeability of the epithelial barrier by inhibiting the expression of mucin 2 and upregulating the concentrations of TLRs and LPS, but also activates the mTOR, which further causes intestinal dysfunction and the excessive release of proinflammatory cytokines, and the inflammatory response further disrupts the balance between Treg and Th17 cells in the intestine, ultimately leading to an increased risk of IBD. The high-glucose diet increases the permeability of the epithelial barrier and the sensitivity of proinflammatory cytokines, and activates TGF-$\beta$ by upregulating the production of ROS in T cells, thereby promoting the differentiation of Th17 cells and ultimately triggering IBD. The high-fat diet could increase oxidative stress in the ER of goblet cells and decrease the expression of mucin 2 and claudin1, thereby disrupting the intestinal barrier and triggering an inflammatory response, and further disrupting the balance between NK T and Treg cells, ultimately exacerbating IBD. The high-salt diet could destroy the colonic barrier by reducing the expression of mucin 2, occluding, and ZO1, which induces excessive release of proinflammatory cytokines, thereby activating the p38/MAPK signaling pathway, disrupting the balance between Treg and Th17 cells and ultimately aggravating IBD. In addition, p38/MAPK can activate SGK1, which promotes the accumulation of salt in the colon via epithelial sodium channels (ENaC) and triggers a proinflammatory "vicious cycle." →: Pro; ⊣: Anti. ENaC, epithelial sodium channels; ER, endoplasmic reticulum; IBD, inflammatory bowel disease; MLKL, mixed lineage kinase domain like pseudokinase; mTOR, mammalian target of rapamycin; $Na^+$, sodium; NFAT5, nuclear factor of activated T cells 5; NK T cells, natural killer T cells; P, phosphorylate; p38/MAPK, p38/mitogen-activated protein kinase; RIPK3, receptor-interacting serine-threonine kinase 3; RORC, retinoic-acid-related orphan nuclear receptor C; RORγt, retinoid-related orphan nuclear receptor γ t; ROS, reactive oxygen species; SGK1, serum glucocorticoid kinase 1; TGF-$\beta$, transforming growth factor-$\beta$; Th17, T helper 17 cells; TLR, Toll-like receptor; Treg, regulatory T cells; TRIM11, tripartite motif containing 11; ZO1, zonula occludens 1.

factor-$\beta$ (TGF-$\beta$) by upregulating reactive oxygen species (ROS) in T cells, thereby promoting the differentiation of Th17 cells and triggering colitis in mice (18), as illustrated in Figure 1. Similarly, a high-protein or high-fat diet was shown to increase oxidative stress in the endoplasmic reticulum (ER) and decrease the expression of Muc2 and claudin 1 in the colon tissues of mice, thereby disrupting the intestinal barrier and triggering an inflammatory response, and further disrupting the balance between nonclassical natural killer T cells and Treg cells, ultimately exacerbating experimental colitis (47, 48), as summarized in Figure 1.

## High-salt diet

The high-salt diet (HSD) is generally defined as a diet that includes a total salt intake of >6 g per day (49), the current average global daily intake of sodium is between 5 and 6 g (equivalent to ~12–15 g of salt), which is nearly 3 times the amount recommended by the WHO (50). The only clinical study ($n$ = 3,220,247) of salt consumption and IBD risk showed that dietary supplementation with potassium ($P_{trend}$ = 0.005) was negatively correlated with the risk of IBD (51). A number of studies have investigated the effects of salt on experimental colitis in various mouse models (19, 52, 53), suggesting that salt is a potential dietary risk factor for IBD. This is mainly because salt may accumulate in the colon of mice, which has a direct effect on colitis, and the excessive production of IL17 triggers an inflammatory response in the colon (54, 55). In addition, an HSD could destroy the colonic barrier by reducing the expression of occludin, zonula occludens 1 (ZO1), and Muc2, and aggravate experimental colitis in mice by activating the p38/mitogen-activated protein kinases (p38/MAPKs) signaling pathways,

disturbing intestinal immune homeostasis, and stimulating the intestinal Th17 response, but inhibiting the function of Treg cells (19, 52, 53). The potential mechanisms of the HSD on IBD are illustrated in Figure 1.

### MED

The MED is a mostly plant-based dietary strategy that is considered to be among the healthiest dietary patterns (56). The MED encourages a high consumption of vegetables, fruits, beans, nuts, and whole grains and moderate consumption of seafood, red wine, and olive oil (57). A meta-analysis showed that a high consumption of fruits could reduce the risk of CD (OR: 0.57, 95% CI: 0.44–0.74, $n = 10$ studies) and UC (OR: 0.69, 95% CI: 0.49–0.96, $n = 8$ studies) and that a high consumption of vegetables is negatively correlated with the risk of UC (OR: 0.71, 95% CI: 0.58–0.88, $n = 9$ studies) (58). A large prospective cohort study ($n = 83{,}147$) with 17 y of follow-up revealed that a higher modified MED score was related to a lower risk of late-onset CD ($P_{trend} = 0.03$) but not UC ($P_{trend} = 0.61$) (11). A recent systematic review conducted by Tian et al. implied that a high score on the MED was inversely associated with the risk and development of IBD (59). The MED can reduce intestinal permeability (60) and benefit patients with IBD after pouch surgery by decreasing calprotectin concentrations and modifying intestinal inflammation (61).

The MED is a balanced nutritional diet that features the high and frequent consumption of fibers (such as grains, vegetables, and fruits) and antioxidants [such as wine and extra virgin olive oil (EVOO)] (62). A prospective study ($n = 170{,}776$ women) with 26 y of follow-up indicated that a long-term intake of dietary fiber, especially from fruits, resulted in a 40% reduction in the risk of CD (63). Desai et al. (64) found that the regular consumption of dietary fiber protects the intestinal mucus barrier, inhibits pathogenic infection, and reduces the incidence of colitis in mice, whereas a fiber-free diet has the opposite effects. Valcheva et al. revealed that a 15 g/d dose of inulin-type fructans was beneficial in patients with mild/moderately active UC (65). Singh et al. (66) recently examined the effects of various dietary fibers on colitis in mice and found that inulin aggravated the severity of IL10 receptor-induced colitis, in part by the activation of NOD-, LRR- and pyrin domain-containing 3 (NLRP3), whereas pectin alleviated colitis. Another study suggests that different types of fibers have differing effects on IBD, which may depend on the existing baseline gut microbiota (67).

Wine and EVOO have been widely studied as the main antioxidant ingredients in the MED. Previous studies have shown that the regular consumption of moderate doses of wine (especially those rich in resveratrol and proanthocyanins) could protect against DSS-induced experimental colitis (68, 69). EVOO is considered to be one of the main contributors to the MED's health benefits (70), because of its potential for antioxidant, anti-inflammatory, and immunomodulatory activities. A diet rich in EVOO could reduce the inflammatory cascade via upregulation of peroxisome proliferator-activated receptor-$\gamma$ (PPAR-$\gamma$) and annexin A1, and inhibition of the activators and signal transducer of STAT3, NF-$\kappa$B, and MAPK signaling pathways, respectively, thereby decreasing the proportion of $CD4^+ROR\gamma t^+$ cells (Th17 cells) expressing $IFN\gamma^+IL17^+$, inhibiting the concentrations of IFN-$\gamma$ and IL17, and ultimately relieving colitis in mice (71–74). The potential mechanisms of the MED on IBD are summed up in **Figure 2**.

### Vegetarian diet or SVD

A vegetarian diet (VD) is characterized by a high consumption of cereals, pulses, nuts, fruits, and vegetables, and exclusion of meat, poultry, and fish (75), whereas an SVD allows eggs, milk, and halved fish (weekly) and all meat (fortnightly) (12), both are plant-based dietary patterns that are usually rich in dietary fiber but low in protein. A case-control study conducted in Canada indicated that the imbalance in the intake of fatty acids, vegetables, and fruits is related to an increased risk of CD in children. More specifically, the higher consumption of long-chain $\omega$-3 fatty acids (OR: 0.44, 95% CI: 0.19–1.00, $P < 0.001$), vegetables (OR: 0.69, 95% CI: 0.33–1.44, $P = 0.03$), and fruits (OR: 0.49, 95% CI: 0.25–0.96, $P = 0.02$) was significantly correlated with lower risks of CD (33). In contrast, the considerable intake of vegetables and fruits seemed to reduce the risk of CD (RR: 0.36 and 0.66) and UC (RR: 0.30 and 0.38) (76). Recently, Khorshidi et al. performed a meta-analysis, and the results indicated that a healthy dietary pattern, characterized by a high intake of vegetables, fruits, dietary fiber, etc., could reduce the risk of CD (OR/RR: 0.39, 95% CI: 0.16–0.62, $P = 0.014$) but not UC (77). A few prospective studies highlighted that a VD or SVD can serve as a protective factor against IBD [OR: 0.29, 95% CI: 0.27–0.39 (UC); OR: 1.179, 95% CI: 0.88–1.57 (CD)] (78), and CD patients following an SVD had a remission rate of 92% at 2 y, and a significantly lower cumulative relapse rate than the omnivorous group ($P = 0.0003$) (12), which could reduce the incidence of CD complications relative to a diet containing meat (42.4% compared with 60.5%, $P = 0.039$) (79). An SVD also has the potential to assist IBD drugs in reducing the relapse rate of IBD (80). Although the exact mechanism of these observed benefits has yet to be determined, a plant-based diet exerts anti-inflammatory effects (81), as shown in Figure 2. A case-control study from Iran found that the dietary inflammatory index was positively associated with the risk of UC ($P = 0.04$) (82). Therefore, the consumption of plant-based foods rich in fiber and phytochemicals is a potential strategy to reduce the occurrence of UC. Although a vegetarian lifestyle can improve the health of adults, it may also bring certain risks, such as lower blood pressure (83) and nutritional deficiencies (84). Therefore, a VD or SVD must be carefully designed to provide adequate nutrition to avoid the risk of malnutrition, and additional randomized controlled trials are still needed to confirm their efficacy and safety in patients with IBD.

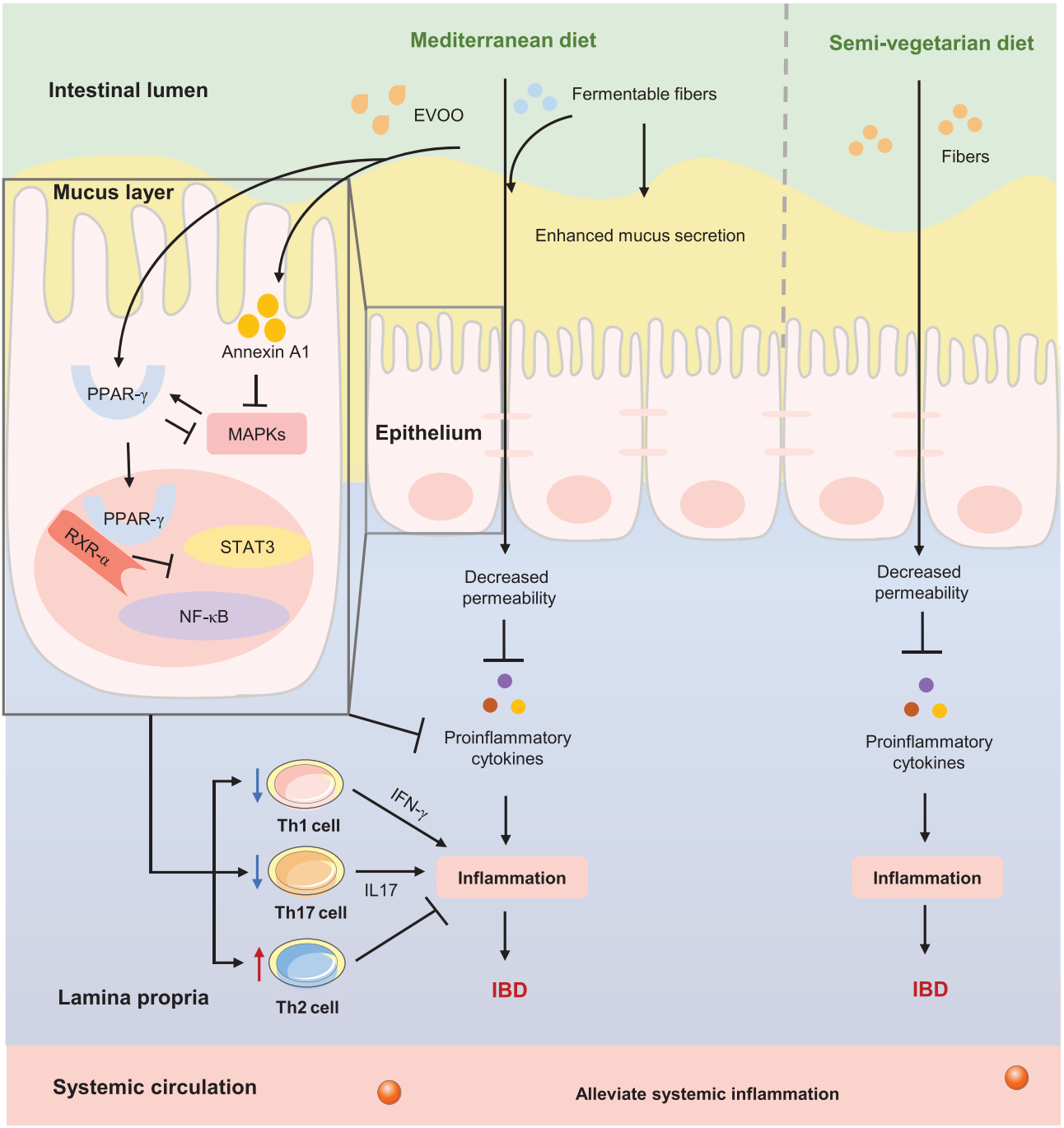


**FIGURE 2** Potential mechanisms of plant-based diets on IBD. Fermentable fibers (such as pectin) in the Mediterranean diet could enhance the secretion of mucus and decrease the permeability of the epithelial barrier, which in turn inhibits the inflammatory response. EVOO in the Mediterranean diet could reduce the inflammatory cascade by upregulating PPAR-$\gamma$ and annexin A1, which in turn inhibits the activators and signal transducers of STAT3, NF-$\kappa$B, and MAPK signaling pathways, respectively, thereby decreasing the proportion of $CD4^+ROR\gamma t^+$ cells (Th17 cells) expressing $IFN\gamma^+IL17^+$ and the concentrations of IFN-$\gamma$ and IL17, and ultimately alleviating IBD; fibers in the semivegetarian diet could decrease the permeability of the epithelial barrier, which in turn inhibits the inflammatory response, and ultimately, reducing the risk of IBD. →: Pro; ⊣: Anti. EVOO, extra virgin olive oil; IBD, inflammatory bowel disease; MAPK, mitogen-activated protein kinase; PPAR-$\gamma$, peroxisome proliferator-activated receptor-$\gamma$; RXR-$\alpha$, retinoid X receptor $\alpha$; STAT3, signal transducers and activators of transduction-3; T cell, T lymphocyte cell; Th, T helper.

### SCD

The SCD is not a low-carbohydrate diet, but one that consists mainly of monosaccharides (glucose, fructose, and galactose), solid proteins, fat, nuts, fruits, and vegetables (high ratio of amylose) but excludes grains, processed meats, additives (such as emulsifiers, preservatives, etc.), starches (such as wheat, barley, corn, rice, etc.), and most dairy products, except for fully fermented yogurts (85–87). The SCD permits the consumption of only monosaccharides in patients with IBD based on the theory that disaccharides and polysaccharides enter the colon without digestion, resulting in excessive growth of bacteria and fungi and secondary harmful effects (88). Studies have shown that following an SCD can significantly reduce IBD disease activity scores and the incidence of intestinal inflammation (14), and as the duration of SCD treatment increased (from 2 to 13 mo), the patients with IBD experienced mucosal healing (40% mucosal healing rate at 52 wk of SCD) (89) and varying degrees of symptom relief (87). The mechanism by which an SCD affects IBD remains unknown, but it is hypothesized that an SCD could reduce the occurrence of intestinal inflammation by restoring the gut microbiome from a proinflammatory state to a normal state (90). Because an SCD makes an obvious contribution to a positive clinical response in patients with IBD, Obih et al. (14) recommended that patients maintain such a diet for 1 y during active disease and for another year after symptom relief. However, many patients find it difficult to maintain an SCD for the long term, resulting in poor adherence and nutritional deficiencies.

### IBD-AID

The IBD-AID, a modified version of the SCD, was developed by Olendzki et al. (13), is divided into 4 phases, and patients are advised to initially consume soft, well-cooked foods without seeds and to eat more whole foods as their symptoms improve. The IBD-AID encourages the intake of prebiotics and probiotics, but it restricts lactose and refined or processed complex carbohydrates, regulates fat intake (reducing the ratio of SFAs to $\omega$-3 PUFAs), identifies nutritional deficiencies and food intolerances, and finally improves food texture to increase nutrient absorption and minimize intact fiber. Only 1 small retrospective case series study has been conducted for the IBD-AID, and the results were encouraging. All patients who followed the diet for $\geq$4 wk experienced symptom remission and were able to discontinue $\geq$1 of their medications (13). Peter et al. (91) recently designed a MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial to investigate whether an IBD-AID™ dietary intervention during the last trimester of pregnancy could reshape the microbiome of patients with CD and their infants, thereby reducing the risk of CD in the offspring. Interventional studies of the IBD-AID remain very rare and are limited by age, small samples, and (or) retrospective studies; therefore, a large number of randomized prospective studies are needed to further investigate its efficacy, mechanism of action, and applicability.

### Low FODMAP diet

The low FODMAP diet specifically allows the use of sucrose, but restricts fructose, lactose, polyols, galactose, and fructans, which can exacerbate gastrointestinal symptoms in patients with IBD (92). The theory behind the low FODMAP diet is to eliminate short-chain carbohydrates that can be fermented by the gut microbiota, which results in gas, bloating, abdominal pain, and changes in bowel habits (93). A low FODMAP diet not only improved common symptoms of irritable bowel syndrome (IBS) in patients with IBD (15), but was also shown to relieve gastrointestinal symptoms in 52% of quiescent IBD patients (94) and 96% of IBD patients (95). Recent clinical practice for the treatment of functional gastrointestinal symptoms of IBD released by the American Gastroenterological Association noted that patients with IBD should consume adequate nutrition while following a low FODMAP diet to manage their functional symptoms (96). Patients are advised to follow a strict low FODMAP diet for the first 4–6 wk under the supervision of a dietitian and then to reintroduce moderate FODMAP foods while still controlling the patient's symptoms to avoid the risk of micronutrient deficiencies or malnutrition (97). Recently, de Castro et al. performed a cross-sectional study and found that "traditional + FODMAP" and "snacks and processed foods" were associated with duration of the CD, but not disease stage (98). Systematic studies are still needed to investigate the potential effects of the low FODMAP diet on intestinal inflammation, mucosal healing, and the gut microbiota in IBD patients.

### GFD

The GFD eliminates gluten, which exists mainly in wheat, barley, rye, triticale, and related processed foods, because gluten sensitivity is common in patients with IBD (23.6% and 27.3% of patients with CD and UC, respectively) (99, 100). A cross-sectional study showed that 40 of 145 participants with IBD (27.6%) exhibited nonceliac gluten sensitivity and that 9 (6.2%) followed the GFD, and patients with CD who had self-reported nonceliac gluten sensitivity had higher disease activity index scores than those without self-reported nonceliac gluten sensitivity (101). A clinical study showed that gluten has the potential to directly activate the innate immune system (102). Given the potential immunogenicity and poor absorption of gluten, which can lead to osmotic diarrhea and even malnutrition in patients with IBD (103), it seems reasonable for patients with IBD to try the GFD. Herfarth et al. (16) conducted a cross-sectional study to assess the prevalence of, and adherence to, the GFD in 1647 patients with IBD found that 314 (19.1%) had followed and 135 (8.2%) were still following a GFD. In addition, 65.6% of patients on the GFD experienced relief of $\geq$1 specific clinical symptom related to gluten exposure (such as bloating, diarrhea, abdominal pain, etc.), 38.3% experienced a reduction in severe IBD flares, 23.6% had less need for medication, and 41.5% of patients who were still following a GFD reported good compliance. Taken together, these observations suggest that the exacerbation

of symptoms in patients with IBD may be attributable in part to gluten or wheat sensitivity and that the GFD has potential benefits for patients with IBD (especially CD). This is mainly based on the following 2 hypotheses, one is that gluten causes inflammation, and the alternative hypothesis is that gastrointestinal symptoms are caused by noninflammatory mechanisms, and more specifically, that IBD-related malnutrition, inflammation, and anatomical structural changes lead to abnormal digestion of wheat-related compounds (104). However, long-term adherence to a GFD can lead to nutritional inadequacies (such as fiber, calcium, and vitamin A, etc.) and a high economic burden (105, 106). Therefore, it is recommended that a GFD be followed only after careful consideration of the potential adverse factors and only under the supervision and guidance of a dietitian.

### Crohn's disease exclusion diet

The Crohn's disease exclusion diet (CDED) is a whole-food diet that includes fruits, vegetables, meats, and both simple and complex carbohydrates, but eliminates certain animal fats, certain types of meats, and reduces exposure to food additives (such as emulsifiers and maltodextrins), as these dietary components can disrupt the intestinal mucus layer or cause dysbiosis (28). Several prospective randomized controlled trials have shown that in children with mild to moderate CD, the proportion of sustained remission was significantly higher in the CDED plus partial enteral nutrition (PEN) than exclusive enteral nutrition (EEN) (107, 108). Recently, a clinical study revealed that both CDED and EEN induce a rapid clinical response (by week 3) and remission in pediatric patients with active CD (109). In addition, CDED with or without combined PEN was equally effective for remission in adults with mild to moderate biologic naïve CD (110).

### Other dietary patterns

There are other dietary patterns that are directly or indirectly related to IBD, including intermittent fasting (IF), fasting-mimicking diet (FMD), paleolithic diet (PD), and ketogenic diet (KD). Although these dietary strategies may not be as well-studied as those listed above, the available data lead us to suspect that these dietary patterns also have the potential to alleviate IBD.

IF is usually a form of an eating pattern that includes a pure water or very low-calorie period of <24 h followed by a normal feeding period of 1 or 2 d (111). A recent study demonstrated that time-restricted fasting and intermittent energy restriction, but not alternate day fasting, could improve intestinal barrier integrity and colon length, relieve intestinal inflammatory responses, alter the composition of the gut microbiota, thereby preventing gut leak, and ultimately reverse the pathological progression of DSS-induced experimental colitis in mice (112), which suggests that appropriate IF may be an effective strategy for nutritional interventions to prevent and treat colitis.

The FMD is a dietary strategy that can be used to maintain a fasting-like physiological state by reducing caloric intake and changing dietary ingredients, but without necessarily fasting (113). Rangan et al. (21) revealed that an FMD can not only relieve intestinal inflammation, accelerate intestinal regeneration, and regulate the gut microbiota in DSS-induced experimental colitis, but also reduce systemic inflammation and the concentrations of immune cells in clinical trials.

The PD consists mainly of lean, nondomesticated meats and plant-based foods, but excludes grains, cereals, refined sugars, domestic meats, and processed fruits and vegetables (114). It is characterized by high intakes of fiber and protein, lower intakes of refined carbohydrates, and comparable intakes of fat (primarily unsaturated fat) and cholesterol, with an emphasis on the source and balance of caloric intake (115). This diet is based on the assumption that modern humans are poorly evolved to adapt to the dietary changes of modern food, and these undigested and agriculturally produced foods contribute to inflammation and ultimately result in modern diseases (116). So far, clinical remission has been reported in only 1 severe case of CD in a patient from Hungary within 2 wk of following a paleolithic ketogenic diet, and this patient remained asymptomatic and off medications for 15 mo (117). However, the PD is accompanied by a risk of deficiencies in folate, calcium, vitamin D, vitamin B-6, and thiamine (103); therefore, reliable scientific evidence should be obtained before this diet is widely advocated.

The KD is a high-fat, low-carbohydrate diet with adequate protein that induces a switch to fatty acid oxidation as an energy source (118). A recent study showed that the KD improved gastrointestinal symptoms and restored fecal calprotectin to the normal range (from 123 to 19 $\mu$g/g) in a patient with UC, but it increased the concentrations of total cholesterol and LDL cholesterol (119). The KD could alleviate gastrointestinal inflammation not only by inhibiting NLRP3 inflammasome activity (120), and promoting intestinal stem cell regeneration and gut healing (121), but also by promoting intestinal immune system homeostasis via excessive secretion of bile acids (BAs) (122). As the KD is a high-fat diet, it is necessary to track the serum lipids of those who follow it.

## Gut microbiota and IBD

### *Alterations of the gut microbiota and function in patients with IBD.*

Growing evidence suggests that the gut microbiota is a crucial actor in IBD (123, 124). This is supported by the finding that colitis is not spontaneously induced in genetically susceptible mice in sterile facilities (125), whereas the fecal microbiota of mice with colitis can induce colitis in normal mice (126). Numerous studies have paid attention to alterations in the composition of the gut microbiota during the development of IBD. These studies have shown reduced fecal and mucosal microbial diversity in IBD, and disturbance of the species composition, which is characterized by a reduction in beneficial bacteria and an increase in pathogens (30, 124, 127–130).

At the phylum level, Firmicutes were markedly reduced in IBD patients, whereas Proteobacteria presented the opposite trend, and inconsistencies in the abundance of Bacteroidetes have been seen in different studies (131–133). At the genus or species level, *Clostridium* and *Escherichia* were commonly increased, whereas *Phascolarctobacterium*, *Faecalibacterium*, and *Roseburia intestinalis* were markedly decreased in IBD (22, 124, 129, 130, 134). Intestinal inflammation can alter gut microbiota and induce dysbiosis, which is characterized by a marked decrease in the representation of obligate anaerobic bacteria and an increased relative abundance of facultative anaerobic bacteria. The generation of S-oxides, N-oxides, and nitrate as by-products of the host inflammatory response selectively enhances growth of facultative anaerobic bacteria (135). For example, the inflammatory host response selectively enhances growth of commensal Enterobacteriaceae, especially *Escherichia coli* (*E. coli*) by generating nitrate (136). Of note, epithelial-derived ROS enable *AppBCX*-mediated aerobic respiration of *E. coli* during intestinal inflammation (137). Previous studies have indicated that alterations in colonocyte metabolism allows the outgrowth of pathogenic bacteria due to increased oxygen in the gut lumen (138). The details of abnormal gut microbiota associated with IBD are summarized in **Table 1**. In summary, in CD patients, *Roseburia intestinalis* were consistently decreased, whereas *E. coli* were consistently increased, and the abundance of *Ruminococcus gnavus* was inconsistent in different studies. *Faecalibacterium* were commonly reduced in CD and ileum Crohn's disease (ICD) patients but increased in colonic Crohn's disease (CCD) patients. *Faecalibacterium prausnitzii* were commonly decreased in CD and UC patients. *Roseburia* were decreased in ICD patients, whereas inconsistent abundance of *Roseburia* and *Shigella* were observed in IBD (CD and UC) and ICD patients, respectively. Rehman et al. (139) speculated that *Faecalibacteria* and *Papillibacter* could be used as "microbiomarkers" for IBD, because they show a consistent pattern of reduction in disease status. However, the reduction in *Papillibacter* has only been demonstrated in that study to date and this finding has not yet been reproduced.

Imbalance of the microbiota in patients with IBD can affect the basic metabolism, the abundance of virulence factors, and antibiotic resistance (129, 140, 141). For example, the basic metabolism (such as amino acid biosynthesis and carbohydrate metabolism), the production of SCFAs, and pyruvate synthase were substantially reduced in patients with IBD, whereas biosynthesis and transport of compounds that favor oxidative stress (such as sulfate transport and glutathione metabolism) were increased. Similar intestinal dysfunction was also found in 2,4,6-trinitrobenzenesulfonic acid-induced experimental colitis in rats (142). In addition, bacterial virulence factors (especially enterotoxins) were found to be significantly enriched in patients with IBD, and most of these virulence factors were derived from *E. coli* and showed a correlation with the abundance of *E. coli* (143). These features imply a "pathogen-like" invasive metagenome. Furthermore, patients with CD showed an increase in the antibiotic resistance protein TolC, which was positively correlated with the abundance of *Escherichia*, whereas one of the most variable antibiotic resistance proteins in patients with UC was cepA (140).

As mentioned above, these results suggest that dysbacteriosis exists in patients with IBD and is characterized by bacteria with less anti-inflammatory capacity and more inflammatory capacity. This can further lead to gut microbiome dysfunction, which mainly includes a reduction in basic metabolism and increased virulence factors and antibiotic resistance. Overall, these results suggest the destruction of the core microbiome and microbiome function in patients with IBD.

***Mechanisms of the gut microbiota contribute to IBD.***
Dysbacteriosis, as a result of decreased diversity of the gut microbiota, has been reported in some patients with IBD, which can affect barrier integrity and the host immune system, leading to chronic inflammation and abnormal immune responses (144). We propose 4 mechanisms by which the gut microbiota may be involved in IBD, including the effects of an imbalance in the microbiota on the expressions of IBD susceptibility genes, the host intestinal barrier, immune function, and physiological metabolism. These mechanisms may contribute simultaneously to the pathogenesis of IBD. The mechanisms of the gut microbiota in the pathogenesis of IBD are summed up in **Figure 3**.

***Gut microbiota, host genes, and IBD.***
More than 200 susceptible loci associated with IBD have been identified to constitute the complex genetic architecture of IBD (145, 146). Researchers have recently begun to focus on the complex interaction between host genetics and the gut microbiota in patients with IBD. The shift in the gut microbiota in genetically susceptible hosts could result in increased susceptibility to IBD (147). It has been reported that the expressions of dual oxidase 2 (*DUOX2*) and *APOA-1* are positively correlated with the abundance of Proteobacteria and Firmicutes, respectively (148). Even in healthy control subjects, the variabilities in IBD genetic risk are related to adverse variations in the gut microbiota. In particular, a reduced abundance of *Roseburia* is associated with an increased number of IBD risk alleles (124). In addition to the influence of the gut microbiota on the expression of IBD risk alleles, certain host genes are also involved in shaping the gut microbiota (32). For example, patients with IBD who carry *NOD2* and *ATG16L1* can exhibit a significant decrease in the abundance of *Faecalibacterium* and an increase in the abundance of *Escherichia* (149). As mentioned above, complex interactions occur between the gut microbiota and host genes, which are involved in IBD susceptibility. However, population-level studies have revealed that host genetics has a minor impact on microbiota composition (150) and IBD is probably not an exception.

**TABLE 1** Overview of changes in the gut microbiota associated with IBD in humans

| Subjects | Samples | Microbiota changes | References |
|---|---|---|---|
| 15 twin pairs for UC<br>23 twin pairs for CD<br>vs.<br>2 healthy pairs | Stool | **Bacteroidetes**<br>*Hallella*▲<br>Prevotella◇<br>Porphyromonadaceae●◇<br>**Proteobacteria**♦<br>Aeromonas♦<br>Citrobacter♦<br>Shigella♦<br>Enterobacteriaceae♦<br>**Actinobacteria**<br>Bifidobacterium▲<br>Collinsella▲<br>**Firmicutes**▲<br>Ruminococcus▲<br>Anaerovorax♦<br>Faecalibacterium▲◇<br>Ruminococcaceae▲◇<br>Roseburia◇<br>Lachnospiraceae◇<br>Peptococcus◇<br>**Tenericutes**○▲◇<br>Asteroleplasma○▲◇ | (134) |
| 75 UC patients<br>121 CD patients<br>8 indeterminate<br>vs.<br>27 healthy controls | Stool | **Bacteroidetes**<br>*Odoribacter*□<br>**Proteobacteria**■<br>Enterobacteriaceae■<br>*Escherichia*◇ *Shigella*◇<br>**Firmicutes**<br>Ruminococcaceae↓<br>Veillonellaceae■<br>*Faecalibacterium*◇<br>*Roseburia*□<br>Leuconostocaceae○<br>*Phascolarctobacterium*□ | (129) |
| 447 CD patients (children)<br>vs.<br>221 healthy controls | Stool | **Bacteroidetes**↓<br>Porphyromonadaceae↓<br>*Bacteroides*↓<br>*Bacteroides vulgatus*↓<br>*Bacteroides caccae*↓<br>**Proteobacteria**↑<br>Neisseriaceae↑<br>*Eikenella corrodens*↑<br>Enterobacteriaceae↑<br>Pasteurellaceae↑<br>*Haemophilus parainfluenzae*↑<br>*Escherichia coli*↑<br>**Actinobacteria**↓<br>Micrococcaceae↑<br>Bifidobacteriaceae↓<br>*Bifidobacterium bifidum*↓<br>*Bifidobacterium longum*↓<br>*Bifidobacterium adolescentis*↓<br>*Bifidobacterium dentum*↓<br>Coriobacteriaceae↓ **Firmicutes**↓<br>Gemellaceae↑<br>*Gemella moribillum*↑<br>*Faecalibacterium*↓<br>*Faecalibacterium prausnitzii*↓<br>Streptococcaceae↑<br>Veillonellaceae↑<br>*Veillonella parvula*↑<br>Christensenellaceae↓<br>Clostridiaceae↓<br>*Clostridium bolteae*↓ | (130) |

(*Continued*)

**TABLE 1** (*Continued*)

| Subjects | Samples | Microbiota changes | References |
|---|---|---|---|
| | | *Clostridium nexile*↓<br>Lachnospiraceae↓<br>*Blautia* ↓<br>*Blautia hansenii*↓<br>Ruminococcaceae↓<br>*Ruminococcus*↓<br>*Ruminococcus gnavus*↓<br>Erysipelotrichaceae↓<br>*Roseburia*↓<br>*Roseburia intestinalis*↓<br>*Coprococcus*↓<br>*Coprococcus comes*↓<br>*Eubacterium rectale*↓<br>**Tenericutes**<br>Verrucomicrobiaceae↓<br>**Fusobacteria** Fusobacteriaceae↑<br>*Fusobacterium nucleatum*↑ | |
| 107 UC patients<br>188 CD patients<br>18 IBDI/IBDU patients<br>vs.<br>582 healthy controls | Stool | **Bacteroidetes**■<br>Porphyromonadaceae↑<br>**Proteobacteria**■<br>Enterobacteriaceae↑<br>*Escherichia coli*■<br>*Shigella*■<br>**Actinobacteria**↓<br>Actinomycetaceae○<br>Bifidobacteriaceae↓<br>Coriobacteriaceae□<br>**Firmicutes**○<br>*Faecalibacterium prausnitzii*□<br>Mogibacteriaceae□<br>Christensenellaceae□<br>Clostridiaceae□<br>Dehalobacteriaceae□<br>Ruminococcaceae□<br>Erysipelotrichacea□<br>Lachnospiraceae○<br>*Roseburia intestinalis*□<br>Peptococcaceae↓<br>Peptostreptococcaceae↓<br>Enterococcaceae■<br>Lactobacillaceae●<br>Aerococcaceae↑<br>**Tenericutes**↓<br>Mollicutes□ | (124) |
| 68 CD patients<br>53 UC patients<br>vs.<br>34 healthy controls | Stool | **Proteobacteria**<br>*Escherichia coli*↑<br>**Actinobacteria**<br>*Bifidobacterium breve*●<br>**Firmicutes**<br>*Coprococcus catus*□<br>*Faecalibacterium prausnitzii* □<br>*Ruminococcus lactaris*□<br>*Roseburia*■<br>*Clostridium symbiosum*●<br>*Clostridium clostridioforme*↑<br>*Lactobacillus gasseri*↑<br>*Lachnospiraceae bacterium*↑<br>*Enterococcus faecium*↑<br>*Ruminococcus gnavus*↑<br>*Pediococcus acidilactici*↑<br>*Blautia producta*↑ | (141) |

■□ Represents a significant increase or decrease in both CD and UC patients, respectively;
●○ represents a **s**ignificant increase or decrease in UC patients, respectively; ↑↓ represents a significant increase or decrease in CD patients, respectively; ▲△ represents a significant increase or decrease in CCD patients, respectively; ♦◇ represents a significant increase or decrease in ICD patients, respectively.
CCD, colonic Crohn's disease; CD, Crohn's disease; IBD, inflammatory bowel disease; IBDI, inflammatory bowel disease intermediate; IBDU, inflammatory bowel disease undetermined; ICD, ileum Crohn's disease; UC, ulcerative colitis.

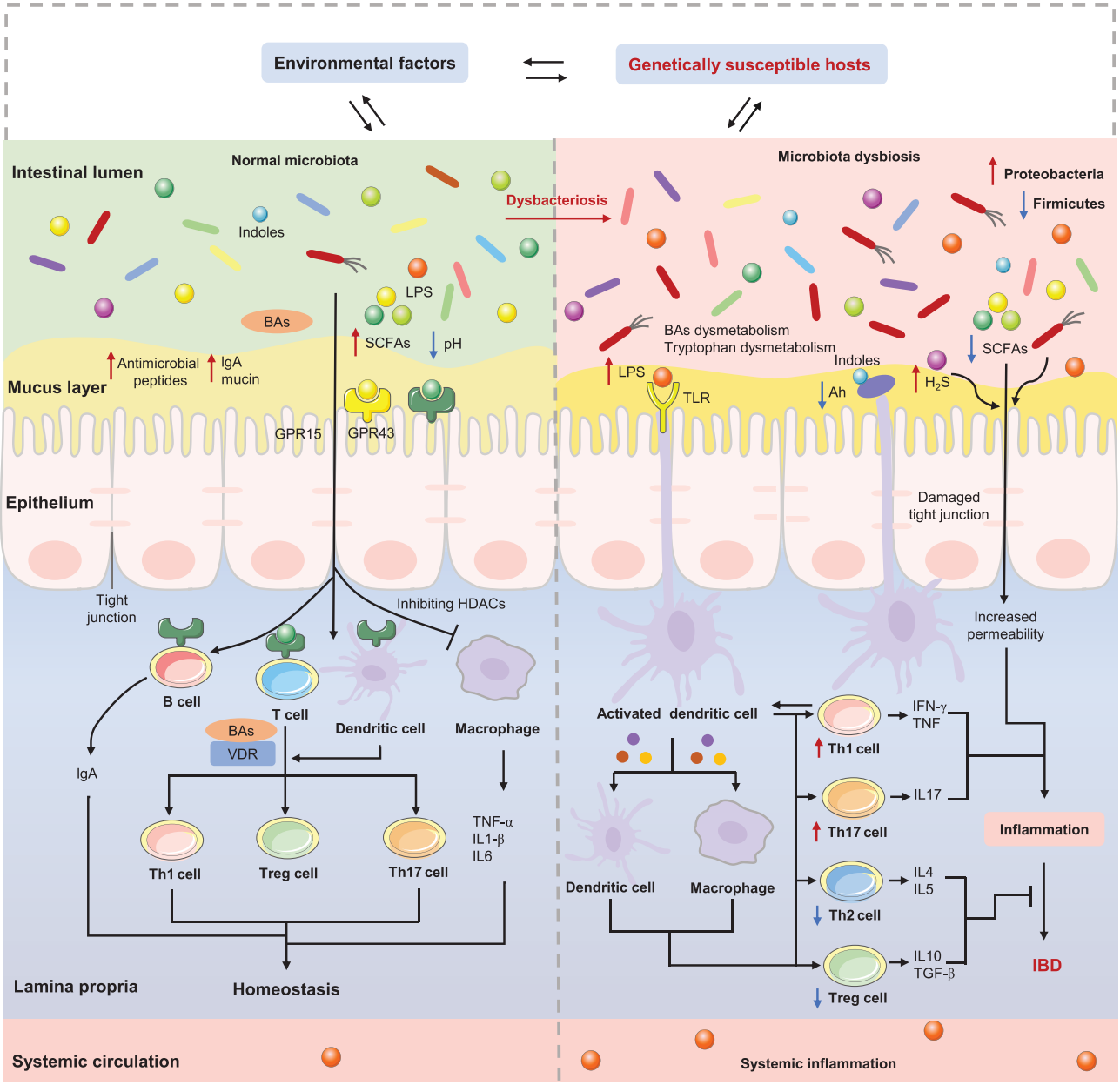


**FIGURE 3** Mechanisms of the gut microbiota in the pathogenesis of IBD. Under normal conditions, the gut microbiota and its metabolites are in a dynamic balance, which contributes to the maintenance of immune homeostasis. In genetically susceptible hosts, certain environmental factors (such as the Western diet) can trigger microbiota dysbacteriosis, which can affect the expressions of IBD susceptibility genes (such as *DUOX2* and *APOA-1*) and further trigger metabolic dysfunction (such as SCFAs, BAs, and tryptophan) and intestinal dysfunction, as well as immune dysfunction, ultimately leading to the occurrence of IBD. →: Pro; ⊣: Anti. Ah, aryl hydrocarbon receptor; B cell, B lymphocyte cell; BAs, bile acids; GPR15, G-protein coupled receptor 15; GPR43, G-protein coupled receptor 43; $H_2S$, hydrogen sulfide; HDAC, histone deacetylase; IBD, inflammatory bowel disease; T cell, T lymphocyte cell; TGF-$\beta$, transforming growth factor-$\beta$; TLR, Toll-like receptor; VDR, vitamin D receptor.

***Gut microbiota, intestinal barrier, and IBD.***
The intestinal barrier is critical for patients with IBD and is closely related to tight junction proteins and the gut microbiota. Turpin et al. performed a prospective study and found that increased intestinal permeability is associated with the later development of CD (151). Decreases in the expression and redistribution of tight junction proteins have been observed in patients with IBD (30, 129, 152). Destruction of the composition of the gut microbiota can affect the interaction between the host and the microorganisms, as well as the intestinal physiology, thereby weakening the intestinal barrier (153). The abundance of *E. coli* is significantly elevated in patients with IBD (130, 141), which can exacerbate barrier dysfunction by destroying

the tight junction proteins, thereby triggering inflammatory responses (154), and ultimately leading to IBD (155). In addition, the increased abundance of sulfate-reducing bacteria in patients with IBD could lead to the production of hydrogen sulfate, which damages intestinal epithelial cells (IECs), increases intestinal permeability, and induces mucosal inflammation (156, 157). Bacterial recognition is dependent on transmembrane pattern recognition receptors, including TLRs and Nod-like receptors (NLRs), the ligation of these bacterial receptors stimulates a series of central signaling cascades (158).

***Gut microbiota, immune function, and IBD.***
The gut microbiota also plays crucial roles in immune maturation and homeostasis. An abnormal gut microbiota has been observed in patients with IBD and can result in alterations of immune system homeostasis (159). Britton et al. (160) recently demonstrated that fecal microbiotas from patients with IBD disturbed $CD4^+$ T cell homeostasis in germ-free mice, which was characterized by an increase in Th2 and Th17 cells and a decrease in ROR$\gamma t^+$ Treg cells, whereas microbiotas from healthy individuals induced more ROR$\gamma t^+$ Treg cells. *F. prausnitzii* and *Bifidobacterium* are significantly decreased in patients with IBD (124, 141), which can modulate the immune response after activating dendritic cells by binding pattern recognition receptors (such as TLRs) via pathogen-associated molecular patterns (PAMPs) (161, 162), subsequently stimulating the corresponding T-cell responses, such as Th1, Th2, or Treg pathways (163). As mentioned above, these studies support the hypothesis that the altered composition of the gut microbiota disturbs the homeostasis between effector T cells and Treg cells (especially Th17 and ROR$\gamma t^+$ Treg cells), and thus contributes to the risk of colitis.

***Gut microbiota, metabolites, and IBD.***
As the vital molecular mediators between the microbiota and host, microbial metabolism has been widely reported to be disrupted in IBD, which is manifested mainly by reduced concentrations of SCFAs (164) and medium-chain fatty acids (165), dysregulation of the metabolism of BAs (2, 141), and alteration of the concentrations of tryptophan (166), amino acids (167), polyamines (168), acylcarnitines (2), triacylglycerols, sphingolipids, and tetrapyrroles (141). The following sections focus on the effects of disorders of SCFAs, BAs, and tryptophan metabolism on the progression of IBD.

The concentrations of SCFAs are significantly decreased in patients with IBD (2), in particular, the decrease in butyrate is consistent with the previously observed depletion of butyrate producers, such as *R. hominis* and *F. prausnitzii* (169). Butyrate is a major energy source for colonic epithelial cells, which can contribute to the homeostasis of epithelial cells with other SCFAs by activating the inflammasome to produce IL18 (170, 171), but it also acts as a natural ligand of PPAR-$\gamma$, which is involved in the interaction between PPAR-$\gamma$ and the host-microbe relationship, thereby preventing inflammation in experimental colitis (172). The positive effects of butyrate were further highlighted by Geirnaert et al. (173), who indicated that supplementation with butyrate-producing bacteria could improve the integrity of the intestinal epithelial barrier in patients with CD. SCFAs act as the primary energy source for IECs (174), which affects the host health primarily via binding to metabolite-sensing G-protein coupled receptors (GPCRs) and (or) inhibiting histone deacetylases (HDACs) (175). Smith et al. (176) revealed that the effects of SCFAs on colonic Treg cells are mediated by GPCR15, GPCR43, and the inhibition of HDAC6 and HDAC9. One of the health effects of SCFAs is a consequent decrease in the luminal pH, which in turn, suppresses pathogenic micro-organisms and increases the absorption of certain nutrients (177). SCFAs are also involved in maintaining the intestinal barrier function, which can improve the integrity of tight junctions (178). Furthermore, SCFAs are also involved in maintaining intestinal homeostasis, which contributes to the growth of epithelial cells, the response of B cells, and the differentiation of T cells (179–181).

BAs, as anti-inflammatory molecules, contribute to lipid absorption and cholesterol homeostasis and serve as signaling molecules to regulate their own biosynthesis (182), energy metabolism (183), inflammatory responses (184), and immune homeostasis (185). The impairment of microbiota enzyme activity (such as Firmicutes-associated bile salt hydrolase) is observed in patients with IBD (186), and leads to alterations in the composition of the luminal BA pool, with an increase in primary BAs (including cholate and chenodeoxycholate) at the expense of secondary BAs, and consequent exacerbation of the intestinal epithelial inflammatory response, thus worsening IBD (187, 188). In contrast, secondary BAs can suppress experimental colitis in mice (189). BAs exert numerous metabolic and immune effects by binding to receptors, such as the farnesoid X receptor, the pregnane X receptor, and the vitamin D receptor (VDR) (190). Microbial BA metabolites modulate the homeostasis of intestinal ROR$\gamma^+$ Treg via the VDR, which in turn, mediates host susceptibility to inflammatory colitis in mice (185). These results support the hypothesis that IBD-associated dysbacteriosis could result in dysmetabolism of the BAs and consequently contribute to chronic inflammation, which suggests that BAs are key actors in the proinflammatory "vicious circle" between the gut microbiota and the host.

Studies have demonstrated that dietary tryptophan deficiency contributes to the deterioration of colitis both in a mouse model and patients with IBD (166, 191). Indoles produced by the gut microbiota that metabolize tryptophan can induce the expression of downstream cytokines by binding and activating the aryl hydrocarbon receptor (Ah), thereby regulating intestinal homeostasis (192). Interestingly, the concentrations of Ah were reduced in the inflamed mucosa of patients with CD (193). In contrast, Ah agonists and Ah-activating strains of *Lactobacillus* can alleviate experimental colitis (194, 195). Commensal *Peptostreptococcus russellii* can

also decrease the sensitivity of colitis, which is attributable to the metabolism of tryptophan to indoleacrylic acid (an Ah agonist) (196). Overall, dysregulation of tryptophan metabolism in patients with IBD exacerbates the progression of IBD, whereas activation of Ah alleviates experimental colitis.

***Diet patterns, gut microbiota, and IBD.***

IBD is a chronic and relapsing intestinal inflammatory disease triggered by environmental factors (such as the diet) and occurs in genetically susceptible individuals who are intolerant to dysbacteriosis (6). The composition of the human gut microbiota is shaped by multiple factors, especially the diet, which can strongly affect the composition and function of the trillions of microbes that reside in the human gut (197, 198), in turn, the nutritional value of food is affected by the composition and operation of the consumer's gut microbiota (199).

***Proinflammatory diets, gut microbiota, and IBD.***

The WD (high-fat, high-carbohydrate, low-fiber), and HSD consistently reduce the abundance of beneficial species (such as *Bifidobacterium* or *Lactobacillus*) and promote the bloom of pathogenic bacteria, such as adherent-invasive *Escherichia coli* (AIEC), which in turn, leads to dysbacteriosis and metabolic dysfunction, resulting in intestinal dysfunction and inflammation, and ultimately exacerbating the development of IBD.

It is well-demonstrated that the WD can cause dysbacteriosis, as characterized by the expansion and colonization of AIEC, an increased abundance of Actinobacteria, and reduced abundance of Bacteroidetes and Firmicutes, resulting in metabolic dysfunction (such as SCFAs and BAs) that in turn, causes intestinal barrier dysfunction and excessive release of proinflammatory cytokines and ultimately exacerbates experimental colitis in mice (17, 200, 201). Abnormal expansion of the AIEC is primarily seen in patients with CD rather than UC, and the concentration of SCFAs is consistently reduced in IBD patients (141, 169, 202). In addition, the abundance of Bifidobacterium (a producer of acetate), which showed a positive correlation with mucus barrier function, is significantly decreased after a WD, whereas the mucus growth rate was restored in mice fed a WD supplemented with *B. longum* (203, 204). The WD promotes colonization with AIEC and leads to chronic inflammation in susceptible mice by enhancing the concentrations of microbial LPS and flagellin, and eventually contributing to the occurrence of IBD (17, 205). A recent study revealed that the activation of mTOR is the basis of intestinal dysfunction and inflammation caused by WD, and the activation of mTOR in the IECs depends on microbial-derived PAMPs (such as LPS and flagellin) (44). A WD rich in saturated (milk-derived) fat uniquely promotes *Bilophila wadsworthia*, which can increase the incidence of colitis in genetically susceptible IL10$^{-/-}$ mice by promoting Th1-mediated immune responses, and the conjugation of taurine and hepatic BAs (206). These studies suggest that WD-induced dysbacteriosis can activate mTOR via microbial-derived PAMPs, which leads to intestinal dysfunction, intestinal inflammation, and immune imbalance, ultimately exacerbating colitis, as illustrated in **Figure 4**.

Previous studies have revealed that the deterioration of colitis in mice trigged by an HSD is related to a reduction in *Lactobacillus* and butyrate, which can promote the expression of forkhead box protein p3 (Foxp3) and the differentiation of Treg (23), whereas the adverse effects of an HSD were not found in germ-free mice, which means that the gut microbiota perform a vital role in the exacerbation of HSD-induced experimental colitis (53). In addition, HSD not only triggers the secretion of IL23R of Th17 cells, thereby inducing pathogenicity (207), but also promotes the secretion of IFN-$\gamma$ of Treg cells, thus inhibiting the activity and function of Treg cells in a serum glucocorticoid kinase1 (SGK1)-dependent manner both in vitro and in vivo (208). As stated above, HSD affects the T cell phenotype and its effector functions in microbiota-dependent and SGK1-dependent manners, which in turn, triggers an inflammatory response and eventually exacerbates colitis, as shown in Figure 4.

***Plant-based diets, gut microbiota, and IBD.***

Both MED (high-unsaturated fats, high-fiber) and VD (high-fiber, low-protein) are plant-based dietary patterns that decrease the abundance of pathogenic bacteria (especially *E. coli*), and consistently increase the abundance of beneficial species (such as *Roseburia* or *Ruminococcus*), thereby increasing the concentrations of SCFAs, which modulate intestinal barrier and immune function, as well as intestinal inflammation, and ultimately alleviate IBD.

The MED has been claimed to exert beneficial effects on the gut microbiota and associated metabolomes, thereby contributing to human health (209). Studies have demonstrated that the MED contributes to decreased concentrations of C-reactive protein (CRP) and fecal calprotectin and normalization of the gut microbiota, which is characterized by a decrease in Proteobacteria and Bacillaceae and an increase in Bacteroidetes, *Streptococcus*, *Clostridium*, and *Roseburia* (a producer of SCFAs, especially butyrate) in patients with IBD (61, 210, 211). The abundance of Bacteroidetes and the concentration of SCFAs were positively associated with MED adherence (212), and good adherence to a MED can reduce the risk of later-onset CD (11). Overall, the mechanisms by which a MED contributes to the alleviation of IBD may be attributable to its ability to normalize the gut microbiota and increase the concentrations of SCFAs, which in turn, improves patient compliance with the MED and modulates the intestinal barrier and immune function, as illustrated in **Figure 5**.

A decrease in microbial diversity, with an increase in Bacteroidetes and a reduction in the proportion of Firmicutes, have been reported in patients with IBD (124, 213). Conversely, the abundance of Firmicutes (especially *Blautia*, *Coprococcus*, *Ruminococcus*, and *Dorea*) in the VD group was higher than that in the meat diet group among patients

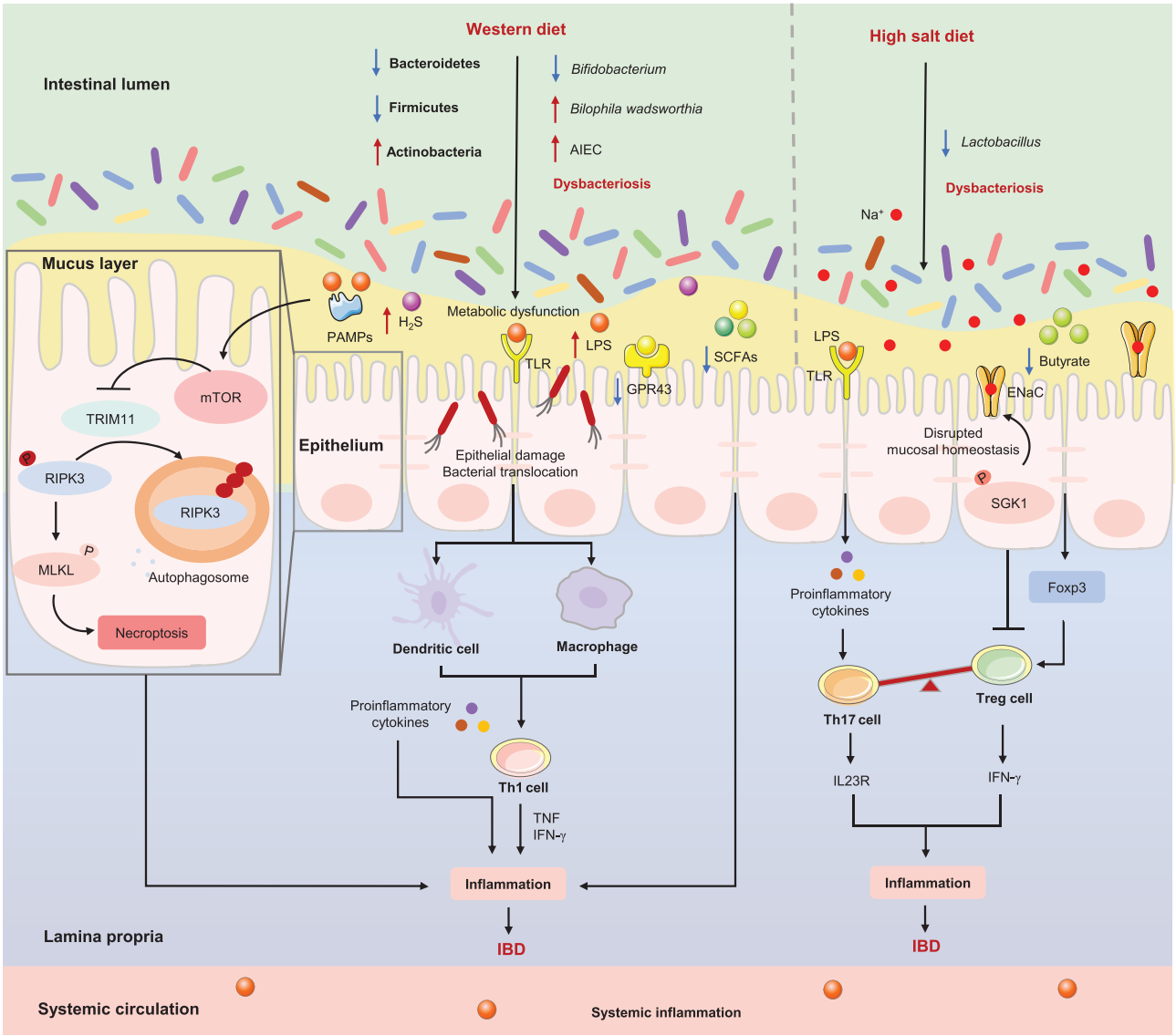


**FIGURE 4** Proinflammatory diets affect IBD by altering certain gut microbiota. The Western diet (WD) promotes the expansion and colonization of AIEC and Actinobacteria, decreases the abundance of Bacteroidetes, Firmicutes, and *Bifidobacterium*, resulting in metabolic dysfunction (for example, $H_2S$, acts as gut mucosal "barrier-breakers" is increased) and the activation of mTOR (depends on microbial-derived PAMPs), thus causing intestinal dysfunction and chronic inflammation, and ultimately contributing to the occurrence of IBD. In addition, a WD could lead to the bloom of *Bilophila wadsworthia*, which can ultimately exacerbate IBD by promoting Th1cell-mediated immune responses. The high-salt diet (HSD) could decrease the abundance of *Lactobacillus* and the concentrations of butyrate (which can promote the expression of Foxp3 and the differentiation of Treg cells). On the other hand, an HSD could affect the T cell phenotype and its effector functions in an SGK1-dependent manner, which in turn triggers an inflammatory response and ultimately exacerbates IBD. →: Pro; ⊣: Anti. AIEC, adherent-invasive *Escherichia coli*; ENaC, epithelial sodium channels; Foxp3, forkhead box protein p3; GPR43, G-protein coupled receptor 43; $H_2S$, hydrogen sulfide; IBD, inflammatory bowel disease; MLKL, mixed lineage kinase domain like pseudokinase; mTOR, mammalian target of rapamycin; $Na^+$, sodium; P, phosphorylate; PAMPs, pathogen-associated molecular patterns; RIPK3, receptor-interacting serine-threonine kinase 3; SGK1, serum glucocorticoid kinase 1; T cell, T lymphocyte cell; Th, T helper; TLR, Toll-like receptor; TRIM11, tripartite motif containing 11.

with UC (79). Dietary fiber from a VD is beneficial for patients with IBD (27, 63), which could be explained by several potential mechanisms. First, dietary fiber contributes to the integrity of the epithelial barrier and the expansion of commensal bacteria, as well as to the limitation of access by pathogenic bacteria (especially *E. coli*) to the gut epithelium, which is called "competitive exclusion" (214, 215). In contrast, an increase in *E. coli* has been observed in patients with CD (124). In addition, fiber from fruits is more soluble or fermentable fiber, which can be metabolized by the gut

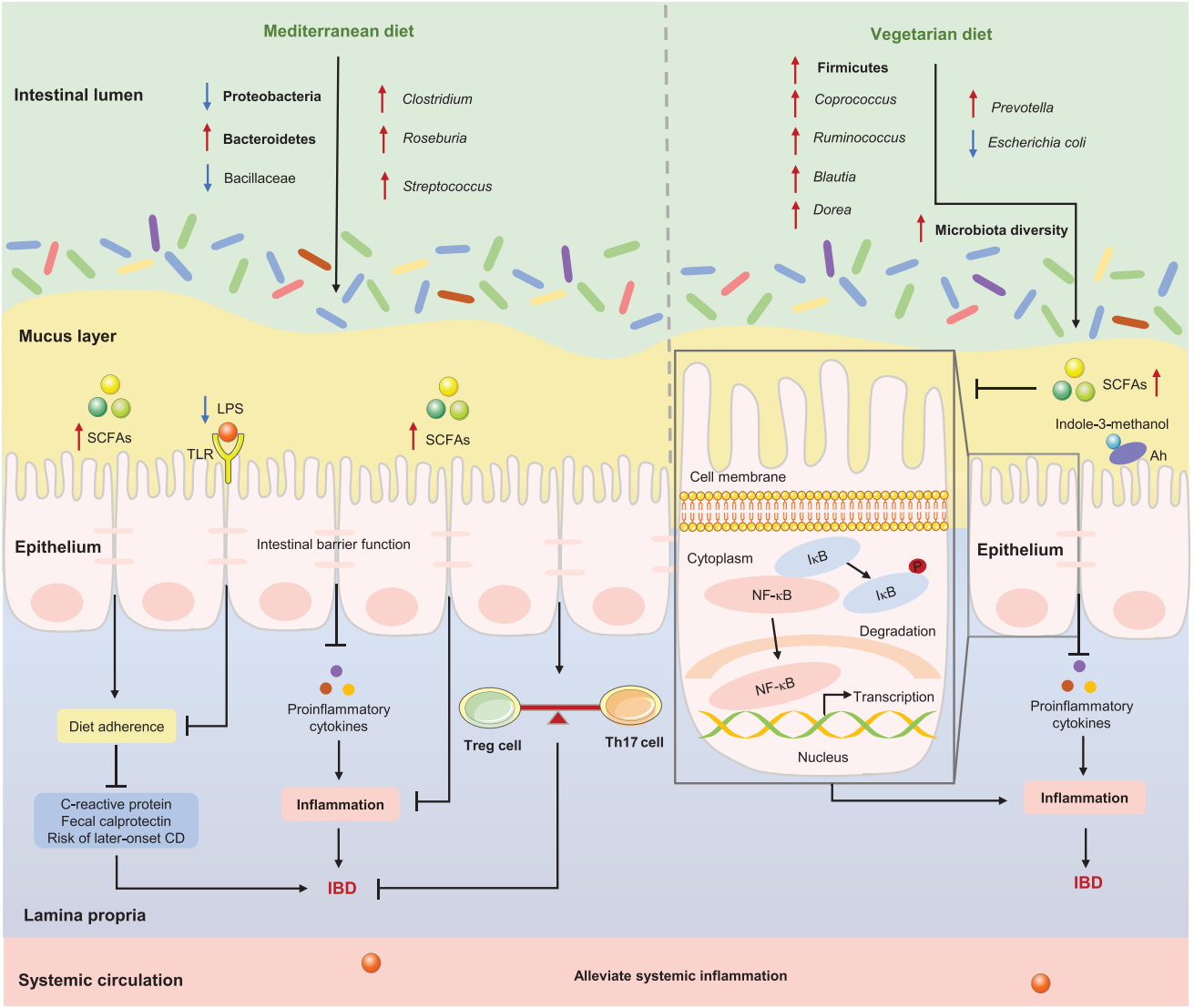


**FIGURE 5** Plant-based diets affect IBD by altering certain gut microbiota. The Mediterranean diet decreases the abundance of Proteobacteria and Bacillaceae, increases the abundance of Bacteroidetes, *Streptococcus*, *Clostridium*, and *Roseburia* (a producer of SCFAs), and thus increases the concentrations of SCFAs. SCFAs can not only improve patient compliance to MED, thereby reducing the concentrations of CRP and fecal calprotectin, and decreasing the risk of later-onset CD, but it also can modulate the intestinal barrier and immune function, ultimately alleviating IBD. The vegetarian diet increases the abundance of Firmicutes (especially *Coprococcus*, *Ruminococcus*, *Blautia*, and *Dorea*), decreases the abundance of pathogenic bacteria (especially *Escherichia coli*), and thus increasing the concentrations of SCFAs, thereby inhibiting the transcription of NF-$\kappa$B and the excessive release of proinflammatory cytokines, ultimately alleviating IBD. In addition, indole-3-methanol, which is present in fruits and cruciferous vegetables, activates the aryl hydrocarbon receptors, thereby reducing the risk of IBD. $\rightarrow$: Pro; $\dashv$: Anti. Ah, aryl hydrocarbon receptor; CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel disease; IκB, inhibitor of NF-$\kappa$B; MED, Mediterranean diet; Th, T helper; TLR, Toll-like receptor; Treg, regulatory T cells.

microbiota into SCFAs, thereby inhibiting the transcription of proinflammatory mediators and NF-$\kappa$B (216, 217). Finally, indole-3-methanol, which is present in fruits and cruciferous vegetables, activates the Ah and attenuates experimental colitis (218). Overall, the benefits of a VD for patients with IBD are a result of the remission of intestinal inflammation by the expansion of commensal bacteria and the limitation of pathogenic bacteria, as well as the increase in SCFAs and indole-3-methanol, as summarized in Figure 5.

***Carbohydrate-restrictive diets, gut microbiota, and IBD.*** SCD, IBD-AID, low FODMAP diet, and GFD are carbohydrate-restrictive diets. Except for the low FODMAP diet, the other 3 dietary patterns increase the concentrations of SCFAs by modulating the gut microbiota, which in turn, inhibits the excessive release of proinflammatory cytokines, and ultimately alleviates IBD. The low FODMAP diet reduces the potentially beneficial bacterial species (especially *F. prausnitzii*), which in turn leads to reduced

concentrations of SCFAs, ultimately increasing susceptibility to colitis.

Few studies have explored the effects of an SCD on the gut microbiota of patients with IBD. Kakodkar et al. (87, 219, 220) demonstrated that patients with IBD who followed the SCD had lower symptom scores, better quality of life, and greater fecal microbiome biodiversity than those who consumed a WD. In addition, a prospective multicenter study of the SCD in children with CD or UC demonstrated that SCD contributes to normalization of CRP (from 24.1 ± 22.3 mg/L to 7.1 ± 0.4 mg/L), an increase in Firmicutes and a decrease in Proteobacteria (221), which expand abnormally in patients with IBD and may cause intestinal inflammation by attacking impaired mucosal surfaces and ultimately exacerbating clinical symptoms (124), as illustrated in **Figure 6**.

Only 1 study has explored the effects of an IBD-AID on the gut microbiota of patients with IBD, showing that *Roseburia* (a producer of SCFAs), which was significantly reduced in IBD patients, increased significantly after the dietary intervention (22), as shown in Figure 6. Furthermore, a reduction of *Roseburia* contributed to the IBD genetic risk score in healthy subjects (124). These results imply that *Roseburia* may be the key bacteria in the prevention and treatment of IBD.

Numerous clinical studies have demonstrated that a low FODMAP diet alters the composition of the gut microbiota in patients with digestive disease (including IBD and IBS), resulting in a reduction in total bacterial abundance (especially *B. longum*, *B. adolescentis*, and *F. prausnitzii*) and an increase in *B. dentium*, and contributes to greater microbial diversity in IBS patients (94, 222, 223). However, the concern is that following a low FODMAP diet may lead to a reduction in SCFAs, which may involve an increased sensitivity of mice to colitis (224). This theoretical concern was confirmed in a randomized controlled crossover feeding trial, which showed that a low FODMAP diet reduced the potentially beneficial bacterial species (especially *F. prausnitzii*) and butyrate in patients with CD (223). A double-blind controlled trial demonstrated that *F. prausnitzii* or its supernatant exerts anti-inflammatory effects on Caco-2 cells and 2,4,6-trinitrobenzene sulfonic acid-induced colitis in mice, which was attributed to the inhibition of NF-$\kappa$B activation and IL8 production (132). Overall, the low FODMAP diet may cause a reduction in *Bifidobacterium* and an increase in fecal pH, which may contribute to the colonization of intestinal pathogenic bacteria and a reduction in anti-inflammatory bacteria, thus aggravating an imbalance in the microbiota, as described in Figure 6. A restrictive low FODMAP diet is not recommended, except during the "induction" phase of prescribed dietary adjustments, because it contributes to the alleviation of functional gastrointestinal symptoms, and patients who do not respond to the diet should stop FODMAP restrictions (94, 225).

A large, prospective, and comprehensive cohort study indicated that the $\alpha$-diversity and *Campylobacter* were significantly increased in patients with CD who followed a GFD, whereas the abundances of *Bacteroides*, *Prevotella*, and *Lachnospira* were significantly increased in patients with UC who followed a GFD (79); however, these bacteria, which are positively associated with the production of SCFAs, were reduced in patients with IBD (134). As a result of reduced SCFAs producers, decreased SCFAs concentrations were frequently observed in patients with IBD (169). SCFAs are currently considered a promising adjunctive therapy for the clinical management of patients with IBD, which can improve clinical symptoms by inhibiting the expression of LPS-induced cytokines and the activation of NF-$\kappa$B (226, 227), as shown in Figure 6. However, the effects of SCFAs intervention are inconsistent in mouse models of experimental colitis, possibly due to differences in species specificity, colitis models, commensal bacteria depletion, butyrate dosing, and administration routes (228). These results suggest that following a GFD has potential benefits for patients with IBD by restoring gut microbiota-metabolism homeostasis, but it should not be recommended for healthy individuals, because a GFD adversely alters the gut microbiome composition, the activity of microbial pathways, and immune function in healthy adult humans (229–231).

### *Other dietary patterns, gut microbiota, and IBD.*

A small number of animal studies have shown that IF (high-carbohydrate, low-fat, low-protein with low calories) and FMD (high-fat, low-carbohydrate, low-protein with low calories) could relieve IBD by regulating the gut microbiota. Although the evidence for these dietary strategies may not be as strong as those mentioned above, based on the available data, we suspect that these dietary patterns may also have the potential to alleviate IBD, which is partly attributable to modulation of the gut microbiota.

A recent study demonstrated that intermittent energy restriction uniquely reduced the enrichment of Peptostreptococcaceae, whereas time-restricted fasting and intermittent energy restriction not only suppressed the abundance of *E. coli* and *Shigella* (both of which were increased in DSS-induced mice), but also promoted the abundance of SCFAs-producing bacteria (including *Ruminococcus*, *Lactobacillus*, and *Coprococcus*), and ultimately increased the production of SCFAs (112). Overall, the potential benefits of IF for patients with IBD may be attributable in part to the suppression of harmful microbiota and the expansion of beneficial microbiota and their related metabolites (especially SCFAs).

Only 1 study has investigated the effects of an FMD on the gut microbiota of DSS-induced colitis in mice (21), and the results showed a noteworthy decrease in *S24-7* and conspicuous increases in Bifidobacteriaceae and Lactobacillaceae, which are involved in the modulation of T-cell activity, thereby alleviating the severity of IBD symptoms in an experimental model (232).

## Conclusions

Dietary patterns can modulate the occurrence and progression of IBD through various signaling pathways, including

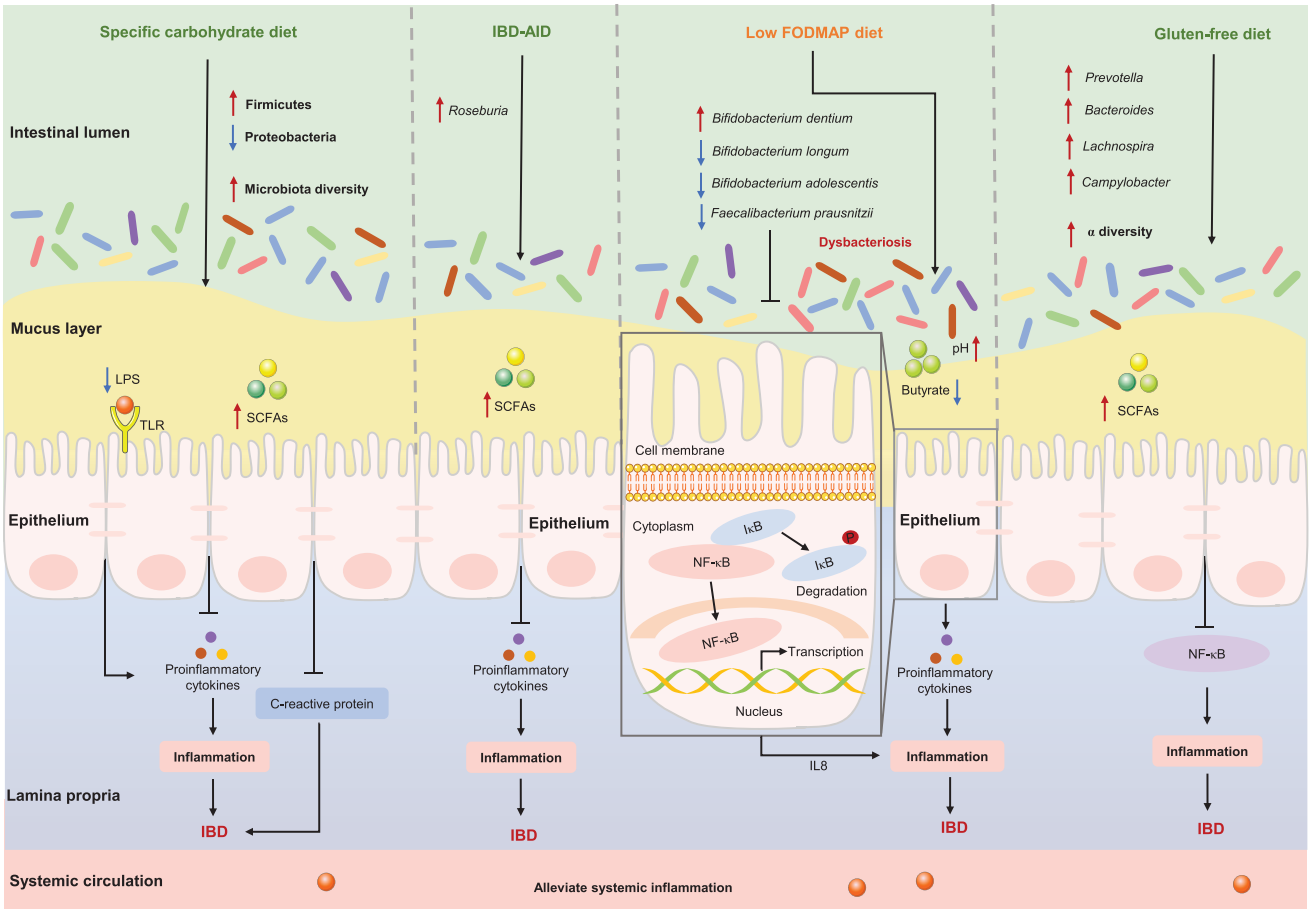


**FIGURE 6** Carbohydrate-restrictive diets affect IBD by altering certain gut microbiota. The specific carbohydrate diet increases the abundance of Firmicutes, decreases the abundance of Proteobacteria, and thus increasing the concentration of SCFAs, thereby reducing the concentrations of CRP and the excessive release of proinflammatory cytokines, ultimately alleviating IBD. The IBD anti-inflammatory diet increases the abundance of *Roseburia* (a producer of SCFAs), thus increasing the concentrations of SCFAs, thereby inhibiting the excessive release of proinflammatory cytokines, ultimately alleviating IBD. The low FODMAP diet increases the abundance of *Bifidobacterium dentium*, decreases the abundance of *Bifidobacterium longum*, *Bifidobacterium adolescentis*, and *Faecalibacterium prausnitzii*, and thus decreasing the concentrations of butyrate. *F. prausnitzii* or its supernatant could inhibit the activation of NF-κB and the secretion of IL8, which in turn suppresses the inflammatory response; The gluten-free diet increases the abundance of *Prevotella*, *Bacteroides*, *Lachnospira*, and *Campylobacter*, thereby increasing the concentrations of SCFAs, which can suppress the inflammatory response by inhibiting the activation of NF-κB, and ultimately alleviates IBD. →: Pro; ⊣: Anti. CRP, C-reactive protein; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide and polyol; IBD, inflammatory bowel disease; IBD-AID, IBD anti-inflammatory diet; IκB, inhibitor of NF-κB; TLR, Toll-like receptor.

mTOR, MAPKs, STAT3, and NF-κB. For example, proinflammatory diets (such as the WD and the HSD) could trigger inflammatory responses and immune imbalances through activation of mTOR and p38/MAPK signaling pathways, thereby exacerbating the progression of IBD. In contrast, the MED could modulate immune function by inhibiting activators and signal transduction of STAT3, NF-κB, and MAPK signaling pathways, thereby ultimately alleviating IBD. In general, IBD patients should avoid excessive intake of animal fats and promote a diet high in fruits and vegetables. It may be wise to maintain a well-balanced and varied diet.

The gut microbiota plays a vital role in the progression of IBD, which affects the expression of IBD susceptibility genes, such as *DUOX2* and *APOA-1*, the intestinal barrier (in particular, the expression of tight junction proteins), immune function (especially the homeostasis between effector and Treg cells), and physiological metabolism, in particular, SCFAs, BAs, and tryptophan metabolism.

Both clinical trials and animal studies support the notion that dietary patterns modulate the onset and progression of IBD, which is partly attributable to modulation of the gut microbiota. Proinflammatory diets such as the WD and the HSD consistently reduce the abundance of beneficial species (for instance, *Bifidobacterium* or *Lactobacillus*) and promote the bloom of pathogenic bacteria (such as AIEC). WD-induced dysbacteriosis can activate mTOR via microbial-derived PAMPs, which leads to intestinal dysfunction,

intestinal inflammation, and immune imbalance, ultimately exacerbating colitis. An HSD affects the T cell phenotype and its effector functions in microbiota-dependent and SGK1-dependent manners, which in turn triggers an inflammatory response and eventually exacerbates colitis. Plant-based dietary patterns, such as the MED and VD, can reduce the abundance of pathogenic bacteria (especially *E. coli*) and consistently increase the abundance of beneficial species (e.g. *Roseburia* or *Ruminococcus*), thereby increasing the concentrations of SCFAs, which modulate the intestinal barrier and immune function as well as intestinal inflammation and ultimately alleviate IBD. Carbohydrate-restrictive diets, including the SCD, IBD-AID, and GFD could increase the abundance of SCFAs-producing bacteria (such as *Roseburia* and *Prevotella*), and thus increase the concentrations of SCFAs, which improve clinical symptoms in IBD patients by inhibiting LPS-induced cytokine expression and NF-$\kappa$B activation. The low FODMAP diet reduces the potentially beneficial bacterial species (especially *F. prausnitzii*), which in turn leads to reduced concentrations of SCFAs, ultimately increasing susceptibility to colitis. Furthermore, the IF and FMD may also have the potential to alleviate IBD. Overall, the potential benefits of the plant-based dietary patterns and carbohydrate-restrictive diets (except the low FODMAP diet) for patients with IBD may be partly attributed to the suppression of harmful microbiota (especially *E. coli*) and the expansion of beneficial microbiota (especially SCFAs-producing bacteria) and the accompanying increased concentration of SCFAs. *Faecalibacteria* as "microbiomarkers" of IBD could be used as a target for dietary interventions that combine top-down and bottom-up approaches to modulate microbial communities with the aim of alleviating IBD.

There is now a broad consensus that a more individualized approach to the treatment of IBD is needed. Attempts have been made to construct microbiota simulation models to predict potential dietary intervention strategies by integrating metagenomic data and metabolomics data from patients with IBD (233). Recently, Sasson et al. presented a viewpoint on the role of precision nutrition in the modulation of microbial composition and function in IBD patients, and provided constructive advice for the design of future research to develop precision nutrition in patients with IBD (234). The continuous development of big data, nutrigenomics, systems biology, bioinformatics, and artificial intelligence (such as machine learning) will contribute to the integration and analysis of clinical data, imaging data, and multi-omics data of patients with IBD, which may contribute to the development of more accurate predictive models to move toward the era of precision nutritional interventions for IBD.

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