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Review Article

High-fat diet induces intestinal mucosal barrier dysfunction in ulcerative colitis: emerging mechanisms and dietary intervention perspective

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Abstract: The incidence of ulcerative colitis (UC) is increasing worldwide, but its pathogenesis remains largely unclear. The intestinal mucosa is a barrier that maintains the stability of the body's internal environment, and dysfunction of this barrier leads to the occurrence and aggravation of UC. A high-fat diet (HFD) contains more animal fat and low fiber, and accumulating evidence has shown that long-term intake of an HFD is associated with UC. The mechanism linking an HFD with intestinal mucosal barrier disruption is multifactorial, and it typically involves microbiota dysbiosis and altered metabolism of fatty acids, bile acids, and tryptophan. Dysbiosis-induced metabolic changes can enhance intestinal permeability through multiple pathways. These changes modulate the programmed death of intestinal epithelial cells, inhibit the secretion of goblet cells and Paneth cells, and impair intercellular interactions. Gut metabolites can also induce intestinal immune imbalance by stimulating multiple proinflammatory signaling pathways and decreasing the effect of anti-inflammatory immune cells. In this review, we critically analyze the molecular mechanisms by which an HFD disrupts the intestinal mucosal barrier (IMB) and contributes to the development of UC. We also discuss the application and future direction of dietary intervention in the treatment of the IMB and prevention of UC.

Keywords: High-fat diet, microbiota dysbiosis, gut metabolites, intestinal mucosal barrier, ulcerative colitis, dietary intervention

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by intestinal mucosal barrier dysfunction [1]. UC has become a global disease. In western countries, the prevalence rate of UC is stable but exceeds 0.3%, while in regions with lower prevalence rates, such as Eastern Europe and Asia, the prevalence is increasing [2]. This may be related to environmental factors such as westernization and modernization of lifestyle. Although the pathogenesis of UC remains to be fully clarified, it is considered to result from the interaction of environmental factors, genetic susceptibility, intestinal barrier dysfunction, symbiotic microbiota disorder, and immune imbalance. The intestinal mucosal barrier (IMB) maintains the stability of the intestinal environment by blocking the invasion of pathogenic antigens and eliciting modest immune response, while IMB dysfunction leads to intestinal inflammation [3]. As an environmental factor, food comes in direct contact with the IMB after entering the colon, which is very important for the functioning of the IMB [4]. The effect of diet on UC has been the focus of many studies.

In the past few decades, a high-fat diet (HFD) has become more prominent, particularly in Asia, largely due to globalization and its convenience [5]. An HFD includes processed food based on animal fats and contains low fiber [6]. Studies have shown that the intake of HFD can aggravate inflammatory infiltration in the colon and even induce UC phenotype in healthy mice [7, 8]. A systematic review of 12 randomized controlled trials found that a high intake of

meat and margarine was associated with an increased prevalence and recurrence of UC [9]. It is generally believed that obesity-related chronic illnesses caused by HFD intake is a critical factor associated with intestinal inflammation. Hildebrand et al., however, found that changes in intestinal microbiota composition in HFD-fed mice were independent of obesity [10]. Additionally, a recent study showed that after transferring the gut microbiota of HFD-fed mice to germ-free mice, the nuclear factor-κB (NF-κB) inflammatory pathway was activated, and this proinflammatory process occurs before weight gain and obesity [11]. These studies suggested that HFD-induced microbiota dysbiosis might also play a significant role in the development of UC. However, the molecular mechanisms underlying these processes have not yet been fully elucidated.

Accumulating evidence suggests that dysfunction of the IMB is the central player in UC caused by dysregulated gut microbiota and their metabolites in an HFD environment. An HFD can lead to alterations in the intestinal microbiota; a 6-month randomized controlled feeding trial found that an HFD reduced the diversity of the intestinal microbiota and the abundance of beneficial bacteria [12]. Another study showed that in the absence of dietary fiber, the intestinal microbiota will rely on mucosal glycoproteins secreted by the host as a nutrient source, thereby resulting in mucus layer erosion [13]. Microbiota dysbiosis secondary to an HFD induces dysregulation of the metabolism of fatty acids (FAs), bile acids (BAs), and tryptophan (TRP). Dysregulated microbiota and their metabolites caused by a HFD can lead to IMB dysfunction by affecting the programmed death of intestinal epithelial cells (IECs), reducing the secretion of goblet cells (GCs) and Paneth cells, impairing intercellular connections, and disrupting the immune balance. Food additives such as sweeteners and emulsifiers contained in an HFD as well as Maillard reaction products (MRPs) such as advanced glycation end products (AGEs) produced during food processing can also damage the function of the IMB [14-17], thus leading to the occurrence and aggravation of UC.

Considering that the dysfunction of the IMB is an early event in UC pathogenesis [18], the knowledge of HFD-induced IMB dysfunction may be valuable to prevent and treat UC. Therefore, in the present review, we focused on the destructive effect of an HFD on the IMB and the related molecular mechanisms leading to the occurrence and aggravation of UC. We follow Hippocrates' principle, "Let food be thy medicine and medicine be thy food", taking the molecular mechanism as the target, and the importance and future development of dietary intervention for restoring IMB function were discussed.

Physiological function of the IMB

The IMB mainly comprises the epithelial and mucus layers between the lumen and lamina propria (**Figure 1**). The epithelial layer is composed of a monolayer of IECs and intercellular connections. IECs are composed of five different types of cells differentiated from intestinal stem cells (ISCs) in the crypt, including absorptive (columnar epithelium) or secretory cells (Paneth, goblet, intestinal endocrine, and tuft cells) [19]. The intercellular connections are composed of tight junctions (TJs), adhesion junctions (AJs), and desmosomes. TJs are the apical intercellular junctions containing transmembrane proteins, including occludin, claudin, junctional adhesion molecule (JAM), and cytoplasmic scaffold proteins Zonula occludens-1, Zonula occludens-2, and Zonula occludens-3 (ZO-1, ZO-2, and ZO-3, respectively). AJs consist of the transmembrane protein E-cadherin and intracellular components α-catenin and β-catenin [20]. Desmosomes link cells through desmosomal cadherins and connect these cell contacts to the intermediate filament cytoskeleton [21]. In the colon, the mucus layer is divided into the outer layer and the inner layer. The outer layer is the habitat of intestinal microbiota, while the inner layer is mainly composed of mucin 2 (MUC2) and antimicrobial peptides (AMPs) secreted by GCs and Paneth cells, respectively. The mucus layer prevents the content of the lumen from coming in direct contact with the epithelial layer [22]. Thus, the IMB forms a physical and chemical barrier to maintain intestinal health.

On the one hand, the IMB separates the luminal antigens from the host immune system, spatially blocks the direct contact between the luminal antigens (including microbiota and their metabolites) and immune cells, and avoids

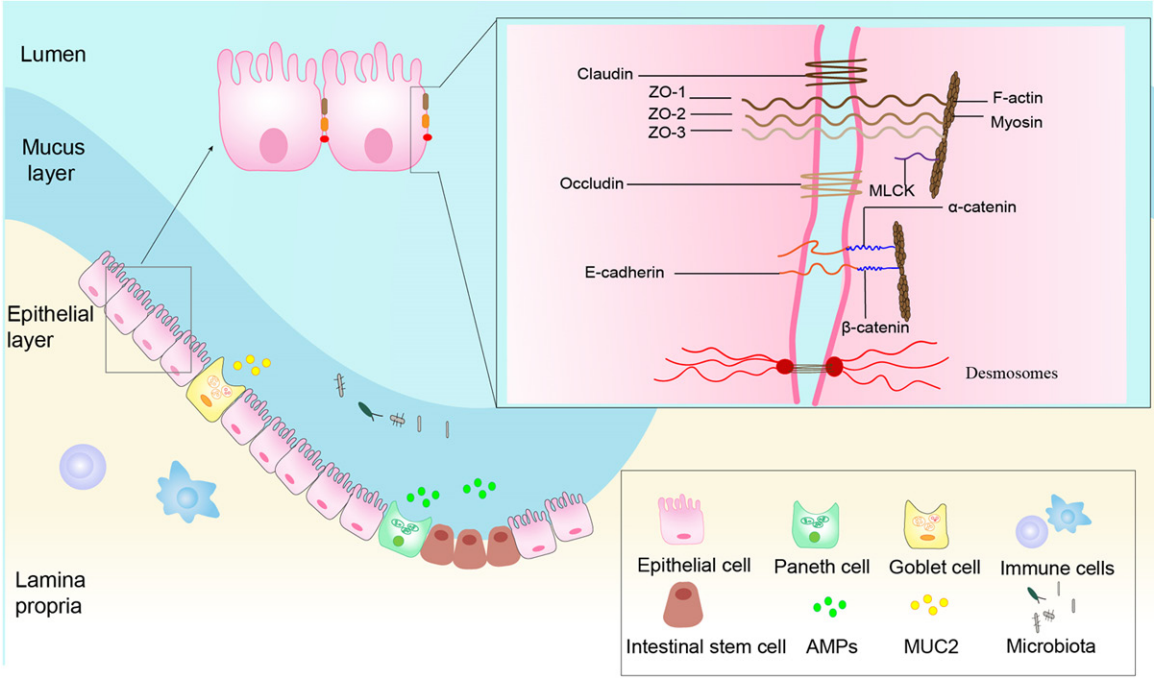

Figure 1. Physiologic structure of the colonic mucosal barrier. The intestinal mucosal barrier is mainly composed of the mucus layer and epithelial layer, and it is affected by intestinal microbiota, its metabolites, and the immune system of lamina propria. The epithelial layer is mainly composed of intestinal epithelial cells (IECs) and intercellular junctions such as tight junctions (TJ), adhesive junctions (AJ), and desmosomes. TJs are the apical intercellular junctions composed of the transmembrane proteins occludin and claudin and cytoplasmic scaffold proteins Zonula occludens-1 (ZO-1), Zonula occludens-2 (ZO-2), Zonula occludens-3 (ZO-3). AJs consist of the transmembrane protein E-cadherin and intracellular components α-catenin and β-catenin. The mucus layer is divided into the outer layer and the inner layer; the outer layer is the habitat of intestinal microbiota, while the inner layer is mainly composed of mucin 2 (MUC2) secreted by goblet cells and antimicrobial peptides (AMPs) secreted by Paneth cells. The IMB forms a physical and chemical barrier between the intestinal lumen and lamina propria, which can "separate" and "regulate" intestinal microbiota and immune cells to maintain intestinal health. MLCK, Myosin Light Chain Kinase.

unnecessary immune reactions and inflammation [23]. A defect in the IMB can weaken this barrier effect. For example, MUC2-deficient mice develop mucous membrane defects, leading to an increase in intestinal mucosal permeability [24]. Similarly, mice lacking AMPs show thinning of the mucus layer and the occurrence of UC [25]. Specific gene knockout in IECs leads to their excessive apoptosis and pyroptosis, and abnormal programmed death of IECs is associated with IMB dysfunction [26, 27]. Mutant mice with a deletion of TJs can develop a UC phenotype [28].

On the other hand, the IMB can sense the signals of microbiota and the immune system so as to regulate microbiota and immune homeostasis. For example, the intestinal bacterial metabolite short-chain fatty acids (SCFAs) can bind to G protein-coupled receptors (GPR41, GPR43, and GPR109A) of IECs, resulting in the activation of the NLRP3 inflammasome in IECs, which in turn release IL-18, regulate innate and acquired immune responses, and thus antagonize the anti-inflammatory reaction [29]. Mice deficient in GPR41 and GPR43 show an abnormally low neutrophil response, resulting in weakened pathogen clearance and subsequently increased intestinal permeability and inflammation [30]. The immune regulation of the IMB mainly depends on humoral immunity dominated by secretory immunoglobulin (sIgA) and cellular immunity dominated by intraepithelial lymphocytes and lamina propria lymphocytes. For example, IECs can transport sIgA through their basolateral membrane by using the polymeric immunoglobulin receptor (pIgR). When plasma cells in the lamina propria produce the dimer IgA complex, this complex combines with pIgR to form sIgA in the intestinal lumen [31]. SIgA can preferentially identify intestinal pathogens to prevent or even reverse

colitis [32]. When pIgR was knocked out in mice, the stability of symbiotic microbiota was disrupted, and the susceptibility to colitis was increased [33]. In cellular immunity, IECs produce thymic stromal lymphopoietin, transforming growth factor-β (TGF-β), and retinoic acid to promote the differentiation of tolerant dendritic cells, thus enhancing the development of adaptive Foxp3+Treg cells [34]. The expression of semaphorin-7A on the basolateral side of IECs can induce macrophages to produce IL-10 and increase the number of Treg cells, while Sema7a-deficient mice show aggravation of colitis [35].

Dysfunction of the IMB is characterized by the weakening of its function of "separation" and "regulation" [36, 37], which mainly depends on the abnormal changes in intestinal content and host immunity. As an environmental pathogenic factor of UC, an HFD can disrupt the IMB and lead to the occurrence and development of UC by affecting intestinal content and host immunity.

An HFD induces gut microbiota dysbiosis and metabolic changes

Gut microbiota

The symbiotic relationship between intestinal microbiota and host helps to maintain the intestinal barrier, regulate intestinal secretion and immune response, and maintain intestinal health [38-40]. The disruption of intestinal microbiota can lead to intestinal diseases, including UC [41]. Intestinal bacteria have different effects on the digestion and metabolism of diet according to different enzymes, and the structure of intestinal microbiota can change according to the change in the diet [42]. A study in humans found that an HFD increased the number of bile-tolerant microorganisms (*Alistipes*, *Bilophila*, and *Bacteroides*) and decreased the number of Firmicutes (*Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*) that metabolize dietary plant polysaccharides [43]. An HFD promoted the colonization of an IBD-associated pathogen called adherent invasive *Escherichia coli* [44]. An HFD also led to the explosive growth of pathogenic bacteria such as *Bilophila wadsworthia* [45]. An HFD increased the number of lipopolysaccharide (LPS)-producing bacteria in the intestine [12]. LPS is mainly produced by gram-negative bacilli and can destroy the intestinal epithelial barrier [46]. Moreover, an HFD reduced the phylogenetic diversity and abundance of beneficial bacteria such as *Akkermansia muciniphila*, *Lactobacillus*, and *Bifidobacterium* [47]. A decrease in beneficial bacteria such as *Faecalibacterium prausnitzii* and *Roseburia hominis* is related to the pathogenesis of UC [48]. However, the description of changes in intestinal microbiota in the HFD environment in the literature is not completely consistent. For example, Wang et al. found that a refined HFD increased the diversity of bacteria [49]; this result seemed to reverse the damage of an HFD. They further analyzed and discovered that other nutrients contained in a refined HFD interfered with the experimental results. Some scholars believe that the differences between individuals led to this inconsistency [50]. We believe that the different types of fats used in various studies are also the reason for this inconsistency. In general, an HFD reduces the abundance of beneficial bacteria, while augmenting barrier-disrupting microorganisms, which undoubtedly worsens intestinal health (**Figure 2**).

Fatty acids

The production of SCFAs is closely related to intestinal microbiota. SCFAs are mainly derived from undigested carbohydrates such as dietary fiber; however, dietary fiber itself is not digested or absorbed by host cells because mammalian cells lack the enzymes needed to degrade them and therefore require fermentation by intestinal bacteria. Different bacteria produce different SCFAs based on fermentation through their enzyme activities. For example, acetic acid is mainly produced by *Blautia hydrogenotrophica* [51]. Propionic acid is mainly produced by *Akkermansia muciniphila* [52]. Butyric acid is mainly produced by *Faecalibacterium prausnitzii* and *Roseburia hominis* [48]. Acetic acid, propionic acid, and butyric acid are the most important SCFAs in the colon. SCFAs have the function of protecting the IMB; in particular, SCFAs can promote the expression of MUC2 secreted by GCs and improve the defense function of the mucus layer [53]. They can also provide energy for IECs to maintain intestinal epithelial function [54]. SCFAs can combine with GPR41, GPR43, and GPR109A of IECs, resulting in the activation of the NLRP3 inflammasome to release interleukin-18 (IL-18) for regu-

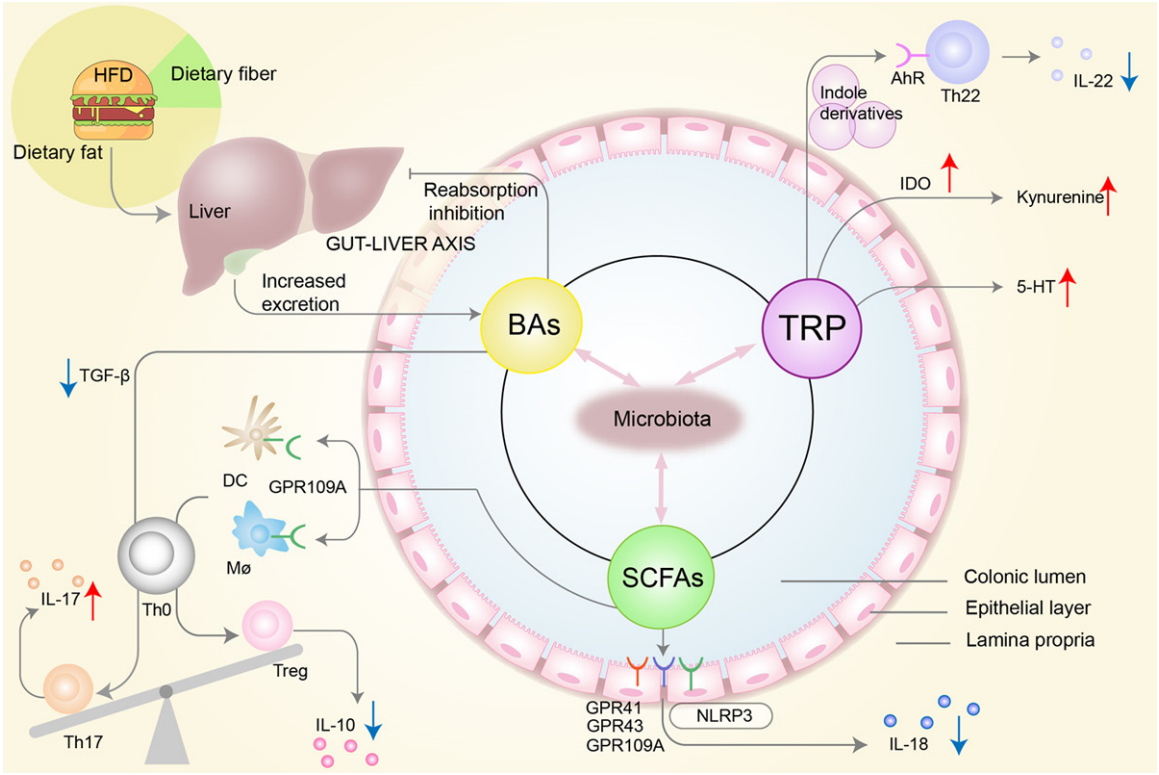

Figure 2. A high-fat diet impairs the metabolic homeostasis of intestinal microbiota, fatty acids, bile acids, and tryptophan in the intestinal lumen. High-fat diet (HFD) contains more animal fat and less fiber, which can disrupt intestinal microbiota and its metabolism. The specific manifestations are as follows: (1) Metabolic disorder of bile acids (BAs), that is, increased production and inhibition of reabsorption of BAs. Abnormal levels of BAs can promote the differentiation of T cells into T helper cells 17 (Th17), resulting in increased interleukin-17 (IL-17) production. (2) The production of short-chain fatty acids (SCFAs) is decreased. SCFAs can bind to G protein-coupled receptors 41 (GPR41), G protein-coupled receptors 43 (GPR43), and G protein-coupled receptors 109A (GPR109A) of intestinal epithelial cells (IECs) and then activate the NLRP3 inflammasome to release interleukin-18 (IL-18). SCFAs also induce T cells to differentiate into regulatory T cells (Treg) and release interleukin-10 (IL-10). Low levels of SCFAs in the colon weaken these pathways. (3) Tryptophan (TRP) metabolism disorder, that is, inhibition of the indole pathway and enhancement of the kynurenine and serotonin pathways, leading to the decrease in interleukin-22 (IL-22) production and the increase in kynurenine and serotonin production. Dysregulated intestinal substances can further disrupt the lamina propria immune system and impair Th17/Treg balance, leading to an increase in proinflammatory cytokines and the decrease in anti-inflammatory cytokines and promoting the occurrence of intestinal inflammation. TGF-β, Transforming Growth Factor-β; DC, Dendritic Cell; Th0, T Helper cell 0; Mφ, Macrophages; 5-HT, serotonin; IDO, Indoleamine 2,3-Dioxygenase.

lating the immune function of the IMB [29]. SCFAs can also activate GPR109A receptors on macrophages and dendritic cells, thereby inducing the differentiation of Treg cells and IL-10-producing T cells [55].

An HFD reduces the concentration of colonic SCFAs [12]. On the one hand, HFD contains less dietary fiber. On the other hand, an HFD reduces the abundance of bacteria that metabolize dietary plant polysaccharides, resulting in a decrease in the content of colonic SCFAs. In addition to SCFAs, the colonic content of other types of fatty acids (FAs) is mainly related to the content of dietary fat in an HFD. A western HFD is mainly composed of animal fat, which contains more saturated fatty acids (SFAs), including long-chain fatty acids (LCFAs), and medium-chain fatty acids (MCFAs) as well as more ω-6 unsaturated fatty acids (PUFAs) [6, 12]. Monounsaturated fatty acids (MUFAs) are mainly found in olive oil; thus, they are less abundant in an HFD [56]. As mentioned earlier, an HFD induces an increase in LPS, which can reduce the absorption of LCFAs and aggravate the colonic accumulation of LCFAs [57]. The accumulation of LCFAs in the colon can lead to an increase in reactive oxygen species (ROS),

which is closely related to the dysfunction of the intestinal epithelial barrier [58]. The ω-3/ω-6 imbalance of PUFAs in the western HFD can also induce intestinal inflammation [59]. However, scientific research has often underestimated the impact of FAs on the colon, based on the fact that the degradation and absorption of dietary fat mainly occur in the small intestine; consequently, it rarely reaches the colon. Tanaka et al., however, found that free FAs induced by an HFD can cause colonic injury at very small doses, which is called "intestinal lipotoxicity" [60]. This implies that even if only a small part of the fat intake reaches the colon, it can have a large impact on the colon (**Figure 2**).

Bile acids

An HFD also affects the metabolism of BAs. Cholesterol is catalyzed by cholesterol 7α-hydroxylase in hepatocytes to produce primary bile acids (PBAs) and stored in the gallbladder; they are then released to the small intestine to participate in the digestion and absorption of lipids. Some BAs may escape to the colon, and under the action of intestinal bacteria (such as *Clostridium scindens*), 7α-dehydroxylation produces secondary bile acids (SBAs). The increase in the level of SBAs is related to the pathogenesis of UC [61]. It was found that an HFD resulted in increased concentrations of total bile acids (TBAs) in the colon as compared to a low-fat or normal-fat diet [62]. Among the TBAs, SBAs such as deoxycholic acid (DCA), taurodeoxycholic acid (TDCA), 12-ketocholic acid (12keto LCA), 3β-DCA, and taurocholate (TLCA) are increased significantly [62]. Several explanations have been suggested for the increase of SBAs in the colon. On the one hand, an HFD itself contains a high level of cholesterol, resulting in a significant increase in PBAs synthesized by the liver, which increases the content of BAs escaping into the colon. On the other hand, an HFD decreases the expression of apical sodium-dependent bile acid transporter (ASBT) and organic solute transporter-α (OST-α), thus inhibiting the reabsorption of BAs by the ileum; this weakens the enterohepatic circulation of BAs and leads to the excretion of a large amount of BAs into the colon [63]. An HFD also reduces the expression of the colonic BA transporters OST-β and ASBT, which inhibits the reabsorption of BAs in the colon [64] and leads to further accumulation of colonic BAs. Abnormally high levels of BAs in the colon, especially DCA, can have several harmful effects on the intestinal mucosa, such as DNA oxidative damage and inflammation, and even lead to the occurrence of colon cancer [65]. An HFD can increase the binding of BAs to taurine to form taurocholic acid [66]. *Bilophila wadsworthia* can metabolize taurocholic acid and promote the production of hydrogen sulfide (H_2S) [67]. H_2S can cause DNA damage in colonic mucosa [68]. BAs and intestinal bacteria interact with each other, and a high concentration of BAs can alter the structure of intestinal microbiota. A study found that the intestinal pool of BAs in HFD-fed mice increased rapidly and significantly within 12 h, and that the microbial composition changed after 24 h [69]. Another study revealed that feeding mice cholic acid (CA) caused changes in the intestinal microbiota similar to those after HFD feeding [70]. A disturbance of intestinal microbiota also affects the metabolism of BAs, with the production of more SBAs and so on as mentioned above, which can aggravate the destruction of the IMB.

Tryptophan

Tryptophan (TRP) is mainly derived from poultry, fish, oats, and dairy products (such as milk and cheese). TRP metabolism in the intestine occurs through three pathways. The kynurenine pathway is the main pathway of TRP metabolism, and it is mediated by indoleamine 2,3-dioxygenase 1 (IDO1); the kynurenine pathway is mainly related to intestinal immunity [71]. The indole pathway can metabolize TRP into indole derivatives, which are the endogenous ligands of aromatic hydrocarbon receptor (AHR). AHR can mediate ILC3 to produce IL-22. Both indole derivatives and IL-22 have a protective effect on the intestinal epithelial barrier [72-74]. The serotonin pathway is mainly related to intestinal motility and secretion [75]. Patients with UC have abnormal TRP metabolism. A study of 535 patients with IBD (including 211 patients with UC) found that the expression of IDO1 and the activation of the kynurenine pathway were increased in patients with UC [76]. A decrease in AHR expression was also observed in patients with IBD [77]. An HFD can directly or indirectly regulate these three metabolic pathways through the intestinal microbiota, thereby disrupting the IMB [78]. An HFD reduced the levels of indole derivatives such as

indole-3-acetic acid (IAA) and indole-3-propionic acid (IPA) [79, 80], which may be related to *Clostridium sporogenes* and *Peptostreptococcus russellii* [81, 82]. Intestinal bacteria such as *Lactobacillus* spp., *Pseudomonas aeruginosa*, and *Pseudomonas fluorescens* have aspartate aminotransferase, which produces kynurenine through the transamination of kynurenine [83]. An HFD can increase IDO1 activity in the kynurenine pathway and shift TRP metabolism from the indole pathway to the kynurenine pathway [84]. This leads to a decrease in indole derivatives and IL-22, thereby causing damage of the intestinal epithelial barrier and inducing intestinal inflammation. In addition, in the serotonin pathway, an HFD can induce *Clostridium ramosum* in the colon to promote the secretion of serotonin (5-HT) by intestinal chromaffin cells [85]. The increase in 5-HT level can aggravate the barrier damage observed in UC [81] (**Figure 2**).

An HFD affects the programmed death of IECs

Apoptosis

The programmed death of IECs is under strict regulation and maintains the normal renewal of cells, while an abnormal increase in the mortality of IECs is the basis for the destruction of the intestinal epithelial barrier and the key to the development of UC. It was found that an HFD could increase the apoptotic rate of IECs [86]. The increased DCA, LCFAs, and LPS in the colon after HFD intake seems to be the culprit of HFD induced cell death, and ROS are involved in this process. DCA can increase ROS production by activating plasma membrane enzymes such as Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and to a lesser extent by activating phospholipase A2, leading to the occurrence of oxidative stress (OS) in colonic IECs, promoting the loss of mitochondrial membrane potential, and inducing the release of proapoptotic factors (caspase-9 and caspase-3) into the cytoplasm. This initial apoptotic step promotes the division of Bcl-2, activates Bax, and forms additional pores on the mitochondrial membrane. Thus, the apoptosis signal is amplified [87]. LPS can activate TLR4 and increase the expression of p53 [88], and p53 increases the expression of Bax and the ROS level, thus inducing apoptosis through mitochondrial signaling pathways [89, 90]. An HFD also promotes apoptosis mediated by the endoplasmic reticulum (ER) apoptosis pathway. The expression of ER stress-associated proteins p-IRE1α and BIP in the colon were found to be increased after a HFD intake [91]. This occurs through the activation of the IRE1α-TRAF2-ASK1 complex by ROS followed by phosphorylation of JNK [92, 93]. JNK can induce apoptosis by controlling the activity of Bcl-2 family members. The activated IRE1α can increase the cytoplasmic Ca^{2+} concentration in the ER, act on mitochondria through the IRE1α-InsP3R pathway, and affect the permeability of mitochondria, leading to a change in mitochondrial membrane potential and promoting the production of ROS [94]. Death receptor pathway-related IEC apoptosis is also involved in the development of UC [95]. DCA can activate the death receptor CD95 and then lead to the cleavage of procaspase-8, activation of promoters of caspase-2 and caspase-8, and induction of cleavage of full-length BH3 interacting-domain death agonist (Bid) [96]. Apoptosis mediated through extrinsic signaling pathways can also be activated by LPS, and this process is largely due to the signal crosstalk between TLR4 and Fas [97]. LPS activates TLR4 and leads to the release of TNF, which can bind to TNFR1 on IECs and induce apoptosis through NFκB2 signaling [98]. A previous study found that the total antioxidant capacity of the colon was lower than that of other intestinal organs [99], and considering the significant role of OS caused by HFD in the process of apoptosis, the increased apoptosis of IECs may have a tremendous impact on IMB dysfunction (**Figure 3**).

Autophagy

The maintenance of IMB function depends on the balance between IEC apoptosis and autophagy. HFD can destroy this balance [100], and this imbalance in turn disrupts the mechanical barrier and induces UC. Recent studies have shown that HFD-fed mice have an accumulation of the colonic autophagy substrate p62 as compared to normal control diet mice [101]. The autophagy substrate p62 accumulates when autophagy is defective, which inactivates the Hippo signal, resulting in the excessive proliferation of ISCs, thus affecting the homeostasis of intestinal epithelium [102]. ISCs with deficiency in autophagy can also lead to mito-

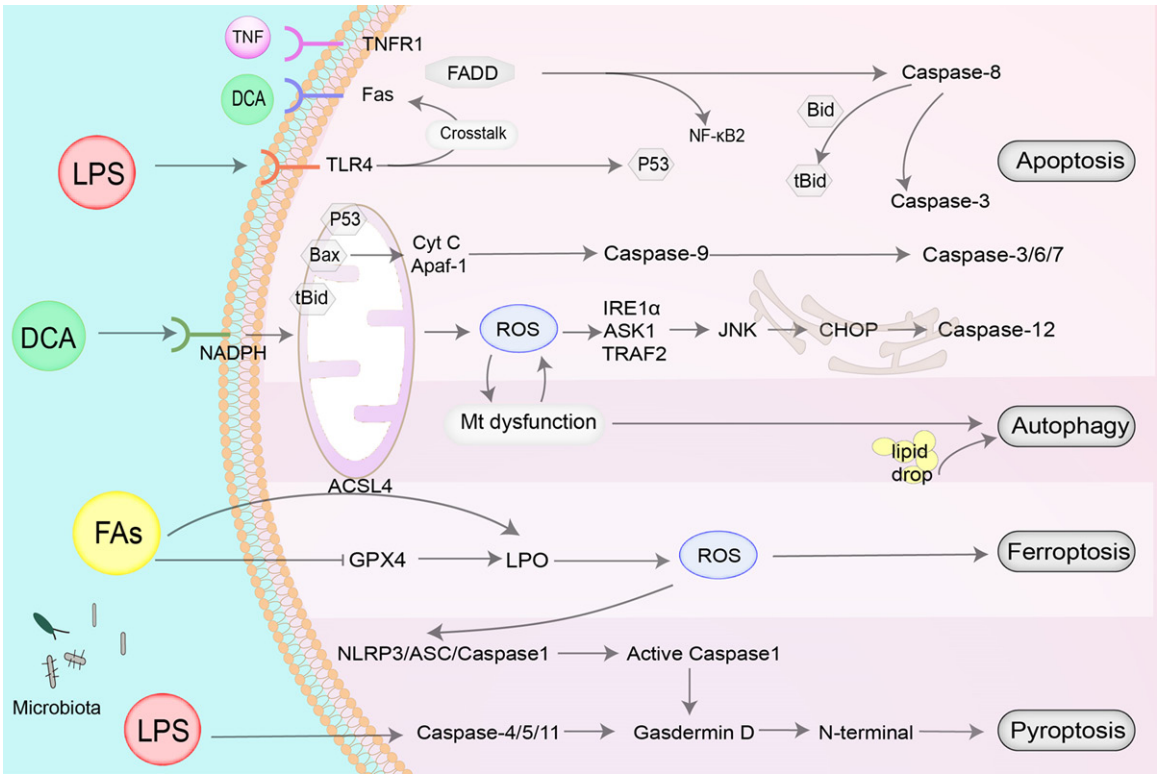

Figure 3. A high-fat diet affects programmed death of intestinal epithelial cells. A high-fat diet (HFD) can change the content of normal intestinal microbiota, fatty acids, and bile acids in the intestine, thus affecting the apoptosis, autophagy, pyroptosis, and ferroptosis of intestinal epithelial cells (IECs). (1) Apoptosis: High levels of deoxycholic acid (DCA), long-chain fatty acids (LCFAs), and lipopolysaccharide (LPS) in the colon can activate the caspase cascade through the mitochondrial pathway, endoplasmic reticulum pathway, and death receptor pathway and then induce apoptosis of IECs. (2) Autophagy: Following mitochondrial autophagy dysfunction and the increase in intracellular lipid autophagy, mitochondria with autophagy disorder can produce more reactive oxygen species (ROS), which will further promote the apoptosis of IECs. (3) Ferroptosis: Fatty acids (FAs) contained in an HFD can inhibit the expression of glutathione peroxidase 4 (GPX4) and increase the expression of acyl-CoA synthetase long-chain family member 4 (ACSL4) in the mitochondrial plasma membrane, resulting in lipid peroxidation (LPO) and ferroptosis. (4) Pyroptosis: An HFD can activate the caspase-1-dependent classical pathway and the caspase-4/5/11-dependent nonclassical pathway. TNF, Tumor Necrosis Factor; TNFR, Tumor Necrosis Factor Receptor; Cyt C, Cytochrome c; Apaf-1, apoptotic protease activating factor-1; NLPR3, NLR family pyrin domain containing 3; ACS, apoptosis-associated speck-like protein containing a CARD; IRE1α, inositol-requiring transmembrane kinase endoribonuclease-1α; ASK1, apoptosis signal-regulating kinase 1; TRAF2, TNF receptor-associated factor 2; JNK, c-Jun N-terminal kinase; CHOP, C/EBP homologous protein.

chondrial dysfunction and increased ROS levels [103]. Increased ROS, in turn, can lead to a mitochondrial autophagy disorder [104], which promotes the occurrence of apoptosis. mTOR-dependent autophagy can be promoted through the upstream TLR4-MyD88-MAPK signaling pathway and the downstream NF-κB pathway, thereby inhibiting intestinal inflammation and epithelial damage caused by increased ROS [105]. Intracellular lipids normally stored in the form of lipid droplets can be degraded and metabolized by autophagy and lysosomal degradation [106]. In the HFD environment, mitochondrial dysfunction can reduce the consumption of FAs [107], and this can also lead to the increase in lipid autophagy in IECs of mice with UC, promote the ability of inflammatory cells to use FAs, and increase the severity of intestinal barrier damage [108]. In conclusion, an HFD may lead to autophagy disorder in IECs, including dysfunction of mitochondrial autophagy, increased intracellular autophagy, and autophagy disorder promoting the occurrence of apoptosis. This suggests that in the HFD environment, restoring the balance between apoptosis and autophagy is very important for maintaining the function of the intestinal epithelial barrier (**Figure 3**).

Pyroptosis

NLRP3-mediated cell death has been found to destroy the intestinal epithelial barrier and lead to intestinal inflammation [109]. HFD intake increases the level of ROS in the colon. ROS can activate the NLRP3/ASC/Caspase-1 signaling pathway, activate the classic pyroptosis pathway of IECs, and lead to the production of the proinflammatory cytokine IL-1β and IL-18 [110, 111]. IL-1β can destroy intercellular junctions and increase the permeability of the intestinal epithelial barrier [23]. IL-18 can inhibit the maturation and secretion of GCs, thus weakening the defense function of the mucus layer and leading to the occurrence of UC [112]. In the HFD environment, LPS produced by gram-negative bacilli is increased in the colon, which activates the caspase-4/5/11 nonclassical pyroptosis pathway [113]. Both caspase-1 and caspase-4/5/11 can cleave gasdermin D to produce an N-terminal fragment [114]; thus, pores are formed on the cell membrane, resulting in the pyroptosis of IECs [115]. The nonclassical pyroptosis pathway induced by HFD has also been found in colonic myenteric nitrogenous neurons, which is related to higher content of LCFAs and LPS in the HFD environment, thereby leading to colonic motility disorders and UC [116] (**Figure 3**).

Ferroptosis

Ferroptosis is a newly discovered programmed cell death that is characterized by ROS accumulation and lipid peroxidation (LPO). Recent studies have shown that ferroptosis is involved in the injury of the intestinal epithelial barrier in UC [117]. The ferroptosis of IECs in UC is related to an abnormality of the nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway and the downregulation of glutathione peroxidase 4 (GPX4) [118]. The Nrf2/HO-1 signaling pathway plays a key role in the antioxidant process, and the activity of GPX4 is the cornerstone of antiperoxide defense [119]. Dietary fat in an HFD, especially PUFAs such as arachidonic acid (AA), can induce impaired GPX4 activity in colonic epithelial cells and increase LPO, thus promoting ferroptosis in IECs [120]. Linoleic acid (c18:2n-6) and α-linoleic acid (ALA; c18:3n-3) can synthesize PUFAs such as AA and adrenic acid (AdA). The intake of AA and AdA could increase the expression of plasma membrane acyl-CoA synthetase long-chain family member 4 (ACSL4). ACSL4 promoted the activation of AA and AdA, followed by iron-dependent lipid peroxidation through the Fenton reaction, resulting in ferroptosis, and the inhibition of ACSL4 could prevent the occurrence of ferroptosis [121]. The inhibition of ACSL4 may therefore be an important intervention to prevent excessive ferroptosis in IECs caused by HFD intake. Because ferroptosis is a newly discovered mode of cell death, especially in an HFD environment, the understanding of the relationship between ferroptosis and UC is only the tip of the iceberg, and more mechanisms and issues need to be addressed (**Figure 3**).

An HFD reduces the secretions of goblet cells and Paneth cells

Goblet cells

GCs are single-cell glands located in the intestinal epithelial layer. They produce and secrete mucin and other substances to make the mucus layer, which forms a mechanical barrier and prevents the invasion of symbiotic bacteria and mucosal inflammation [122]. Microbiota dysbiosis-induced an increase in DCA, and LCFAs trigger programmed cell death of IECs as mentioned above. The loss of GCs further reduces mucin secretion. Mucin is a high-molecular-weight epithelial protein with strong glycosylation activity. An HFD can change the oligosaccharide chain of mouse colonic mucin and lead to the occurrence of UC; the change in mucin composition may be related to a glycosylation defect or tonincomplete maturation of GCs [123]. An HFD can also induce ER stress in GCs through metabolites [124], thus activating the unfolded protein response [128] and decreasing the expression of GC differentiation markers, including Trefoil factor 3, Krüppel-like factor 4, and SAM pointed domain ETS factor 1 [125]; this leads to a decrease in GC number and secretion, accompanied by the increase and metastasis of pathogenic bacteria, which aggravates the susceptibility of epithelial permeability and UC [18, 126]. Increased DCA in the intestinal lumen can also reduce the proliferative function of intestinal stem cells (ISCs) and their ability to differentiate into GCs by triggering ER stress in ISCs [127]. The natural emulsifier soybean phospholipid contained in

an HFD can over-activate the Notch pathway, leading to the depletion of colonic GCs [128]. In conclusion, an HFD can reduce the secretion of GCs by affecting the number and function of GCs, resulting in damage to the IMB.

Paneth cells

The secreted substance of Paneth cells contains a large number of antimicrobial peptides (AMPs), including defensins, lysozyme, and lipopolysaccharide binding protein. AMPs are secreted into the mucosa and react with pathogenic bacteria and proinflammatory cytokines [129]. Paneth cell dysfunction is related to UC [130]. A reduction of AMPs may occur due to the decreased number and impaired function of Paneth cells. An HFD may decrease the number of Paneth cells through programmed death mechanisms as described above. A previous study found that the number of Paneth cells in HFD-fed mice decreased significantly, and the bactericidal activity of the supernatant of Paneth cells also decreased, which was partly caused by lipid-induced cell death [131]. The decrease in the number of Paneth cells is also related to an impaired differentiation of ISCs into Paneth cells. A study showed that an HFD increased the number of Lgr5+ intestinal stem cells by 50%, but decreased the number of Paneth cells by 23%, thus suggesting that an HFD may impair the differentiation of Paneth cells [132]. In addition, the secretory function of Paneth cells may be impaired by metabolites. For example, the expression of AMPs and defensins in HFD-fed mice decreased significantly under BA toxicity [133], which may be related to the destruction of the Mmp7/α defensins axis in the intestine by an HFD [134]. Moreover, the increased production of BAs leads to the upregulation of TGR5 receptors in Paneth cells, and over-activation of TGR5 leads to ER stress, resulting in decreased autophagy and defensin secretion [133]. DCA can inhibit the function of Paneth cells through microbiome changes and excessive signal transduction of farnesoid X receptor (FXR) and type I interferon (IFN) in IECs [135]. In conclusion, an HFD can affect the reduction in the number and function of Paneth cells, thereby reducing the secretion of AMPs and leading to the decline in IMB function.

An HFD induces interruption of intercellular junctions

In all intercellular junctions, tight junctions (TJs) regulate the paracellular transit of water, ions, and molecules and participate in maintaining the polarity of IECs, which is important to maintain the function of the intestinal epithelial barrier. FAs produced by an HFD can directly regulate the distribution and expression level of TJs, thereby disrupting the intestinal epithelial barrier. PUFAs such as γ-linolenic acid (GLA) or docosahexaenoic acid in the colon enhance intestinal permeability through protein kinase C (PKC)-mediated redistribution of the TJ protein, which can be improved by PKC inhibitors [136]. MCFAs such as capric acid (C10) and lauric acid (C12) increase intestinal permeability through the phospholipase C-dependent inositol triphosphate/diacylglycerol pathways; however, capric acid rather than lauric acid leads to redistribution and blocking of the TJ protein ZO-1, thus suggesting that the two MCFAs have partially different mechanisms [137]. Because an HFD contains less fiber, this leads to a reduction in intestinal SCFAs [138]. SCFAs can protect the morphology of ZO-1 and occludin in Caco-2 cells [139] (**Figure 4**).

The dysbacteriosis caused by an HFD will also affect the expression of TJs and destroy the intestinal epithelial barrier. Some intestinal bacteria have been shown to promote TJ protein expression, such as *Bifidobacterium* and *Lactobacillus*, which can enhance the expression of TJ proteins [140]. *Akkermansia muciniphila*-derived extracellular vesicles can also increase the expression of TJ proteins such as occludin to maintain the intestinal epithelial barrier function [141]. The protective effect of these three beneficial bacteria on TJs is, however, reduced in an HFD environment [47, 142]. In contrast, an HFD increased the abundance of *Oscillibacter* [143], which decreased the expression of TJs [144]. In addition, the increased content of bacterial LPS is considered to disrupt the TJ barrier. LPS binds to LBP and is presented to CD14, the receptor for LPS-LBP complexes [145]. LPS-induced TJ barrier damage is related to the adaptor protein MyD88-dependent activation and focal adhesion kinase (FAK) activation in the TLR-4 domain, and the activated FAK in turn leads to the acti-

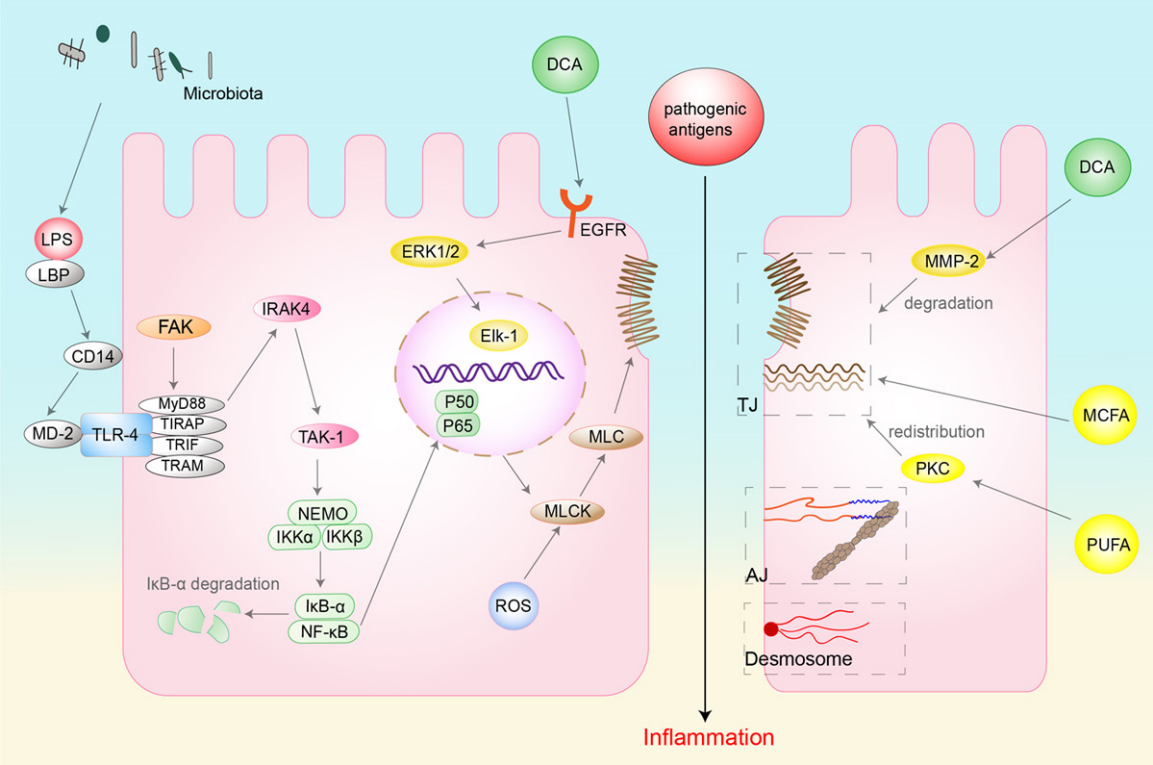

Figure 4. A high-fat diet (HFD) can impair intercellular connections through intestinal microbiota and its metabolites. (1) Intestinal bacterial lipopolysaccharide (LPS) can activate the Toll-like receptor 4 (TLR4) signal transduction pathway, and the nuclear factor kappa B (NF-κB) pathway promotes myosin light chain kinase (MLCK) expression. (2) Deoxycholic acid (DCA) promotes MLCK expression by activating the epidermal growth factor receptor (EGFR) pathway. MLCK can promote the opening of tight junction (TJ) barrier through the phosphorylation of myosin II regulatory light chain (MLC). (3) Fatty acids such as medium-chain fatty acids (MCFAs) and polyunsaturated fatty acids (PUFAs) can disrupt the TJ barrier by altering the distribution and expression of TJs. Finally, this leads to the increase in intestinal permeability, and the pathogenic antigens in the intestinal lumen enter the lamina propria through paracellular permeation, which leads to the occurrence of intestinal inflammation. LBP, lipopolysaccharide binding protein; MD-2, myeloid differentiation 2; FAK, focal adhesion kinase; MyD88, myeloid differentiation primary response 88; TIRAP, Toll/interleukin-1 receptor domain-containing adapter protein; TRIF, TIR-domain-containing adapter-inducing interferon-β; TRAM, translocating chain-associating membrane protein; IRAK4, interleukin-1 receptor-associated kinase; TAK-1, transforming growth factor-β-activated kinase 1; NEMO, nuclear factor-κB essential modulator; IKKα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; ERK1/2, extracellular signal-regulated protein kinase; Elk-1, ETS like-1 protein; ROS, reactive oxygen species; AJ, adhesion junction; PKC, protein kinase C; MMP-2, matrix metallopeptidase 2.

vation of MyD88 and IRAK4. IRAK4 is the downstream target of the TLR-4/FAK/MyD88 signaling axis, and IRAK4 phosphorylation is the signal of TJ barrier opening [146]. The TLR-4/MyD88 signaling pathway is a key upstream regulator of TAK-1 and NF-κB p50/p65 activation. LPS can activate TAK-1 and the classical NF-κB (p50/p65) pathway via TLR-4 [147], and the activated NF-κB (p50/p65) heterodimer can transfer its destructive effects to myosin light chain kinase (MLCK) [148]. MLCK regulates the intestinal TJ barrier function through phosphorylation of myosin II regulatory light chain (MLC) at threonine-18 and/or serine-19, leading to peri-junctional actomyosin ring contraction, mechanical retraction of the apical membrane, pulling apart of the TJ complex, and opening of the intestinal TJ barrier [149] (**Figure 4**).

Deoxycholic acid (DCA) produced by an HFD can also activate the MLCK pathway and destroy the TJ barrier. DCA can activate epidermal growth factor receptor (EGFR) and activate the downstream ERK1/2 signaling pathway. ERK1/2 and the transcription factor NF-κB regulate MLCK together [150]. Especially in an HFD environment, the significantly increased

ROS in cells can promote the activation of the MLCK pathway [151], which further leads to the opening of the TJ barrier. DCA can also destroy the epithelial barrier by affecting the expression of intercellular connexin. DCA can reduce the mRNA levels of 23 genes related to intercellular junction in Caco-2 cells, resulting in damage to the intestinal epithelial barrier [152]. The decreased expression of the TJ protein ZO-1 and occludin induced by DCA may be related to the degradation of TJ protein by MMP-2 [150] (**Figure 4**).

In general, an HFD can directly affect the distribution and expression level of TJs or regulate the expression of MLCK through a signaling cascade, destroy the intercellular connection, and finally lead to the dysfunction of the intestinal epithelial barrier.

An HFD induces immune imbalance

Intestinal mucosal barrier (IMB) damage leads to the entry of pathogenic substances into the lamina propria, causing colitis, which is related to an immune imbalance in the lamina propria. Immune cells such as dendritic cells, macrophages, helper T cells, and regulatory T cells play a key role in the pathogenesis of UC. Studies have shown that an HFD can cause colonic immune cell imbalance, leading to an imbalance between proinflammatory and anti-inflammatory cytokines and thereby promoting colitis [153]. The lethal accumulation of inflammatory cytokines further damages the IMB, causing a vicious cycle. HFD-induced intestinal nervous system disorders can also affect intestinal immunity. Therefore, it is particularly important to pay attention to the effect of an HFD on colonic immune cells.

Dendritic cells

As antigen-presenting cells, dendritic cells can transform the innate immune response to an adaptive immune response. Low levels of butyric acid and retinoic acid in the colon caused by an HFD can lead to the imbalance of subsets of colonic dendritic cells, which is mainly manifested in that the percentage of colon CD103+CD11b+ DCs is 50% lower than that of mice fed a low-fat diet (LFD) [154]. These DC subsets are conducive to Treg differentiation and produce IL-10, which plays an important role in antagonizing intestinal inflammation [155]. However, low levels of SCFAs in the HFD environment weaken this anti-inflammatory effect (**Figure 2**).

Macrophages

The M1 polarization and recruitment of macrophages induced by an HFD are key factors to promote the state of colitis. As mentioned earlier, an HFD leads to increased DCA production. DCA is reabsorbed into the portal vein system by passive diffusion through the colonic mucosa. During its reabsorption, it can contact macrophages in the lamina propria of the colonic mucosa [8]. DCA can induce a significant increase of muscarinic acetylcholine receptor M2 (M2 mAChR) in macrophages and increase the transcriptional expression of TLR2 by targeting the transcription factor AP-1 through M2 mAChR. TLR2 and its downstream NF-κB/ERK/JNK signaling pathway are involved in the induction of polarization of M1 macrophages by DCA [156]. Monocyte chemoattractant protein-1 (MCP-1) expressed in colonic epithelial cells plays a key role in inducing colonic recruitment of proinflammatory macrophages [156]. DCA can induce mouse IECs to express MCP-1 in a dose-dependent manner and induce intestinal recruitment of macrophages [8]. High levels of LPS in an HFD were also found to increase MCP-1 expression in colonic epithelial cells, thereby promoting macrophage recruitment [157]. The Gal-9/Tim-3 pathway plays an important role in infection by regulating macrophage function. Long-term stimulation with LPS can downregulate the expression and secretion of Gal-9, reduce the association between Gal-9 and Tim-3, inhibit the Gal-9/Tim-3 signaling pathway, and finally promote M1 polarization [158].

T cells

The key participant of adaptive immune response is T cells, and abnormal T cell differentiation is an important cause of UC [159]. A previous study showed that an HFD can promote the increase in the secretion of BAs and lead to the FXR target gene (FXRα, Shp, and Ibabp) transforming growth factor β (TGF-β)-dependent downregulation [7]. TGF-β can regulate T-cell differentiation in a concentration-dependent manner with proinflammatory cytokines. When the expression of TGF-β is low, TGF-β,

IL-6, and IL-21 cooperate to promote the expression of the IL-23 receptor (IL-23R) and reduce Foxp3-mediated RORγt inhibition to make the condition conducive to Th17 differentiation. When the expression of TGF-β is high, it can inhibit the expression of IL-23R and contribute to Treg differentiation [160]. An HFD leads to the differentiation of T cells into Th17 by downregulating the expression of TGF-β, thus impairing the Th17/Treg balance. A Th17/Treg imbalance increases the susceptibility to colitis [161]. In addition, because an HFD contains more LCFAs and fewer SCFAs, this study found that LCFAs can promote the differentiation and proliferation of Th1 and/or Th17 cells through the p38 MAPK pathway, while SCFAs can inhibit the JNK1 and p38 pathway, thereby increasing the expression of intestinal Treg cells [162]. When the ratio of ω-6/ω-3 PUFAs is 2:1 or 4:1, it can promote a Th17/Treg balance in patients with colitis and reduce the production of inflammatory mediators. The ratio of ω-6/ω-3 PUFAs as 2:1 is more effective in reducing colitis [163]. However, humans evolved on a diet with a ratio of ω-6/ω-3 essential fatty acids of approximately 1, whereas in western diets, the ratio is 15/1 to 16.7/1 [164]. This severe proportion imbalance in an HFD is not conducive to the maintenance of Th17/Treg balance, which leads to immune disorder and inflammation and disrupts the IMB (**Figure 2**).

Intestinal neurotransmitters

The role of the intestinal nervous system and intestinal immunity has always been a hot topic in the pathogenesis of UC. An HFD can indirectly lead to immune imbalance by affecting intestinal neurotransmitters. Studies have found that an HFD can weaken colonic acetylcholine (ACh) synthesis [165]. ACh promotes IL-10 secretion of monocytic myeloid-derived suppressor cells (M-MDSCs) and inhibits intestinal inflammation by activating the nAChR/ERK pathway [166]; however, low levels of ACh in the HFD environment weakened this protective effect. An HFD induces over-activation of colonic glial cells (EGCs), resulting in the increase in substance P [167]. The concentration of substance P was found to be strongly positively correlated with the concentration of mucosal neutrophils and eosinophils [168]. An HFD reduced the content of vasoactive intestinal peptide (VIP) [169]. VIP is a major immunomodulatory neuropeptide that plays an important role in inflammatory diseases. VIP is considered to be a natural anti-inflammatory agent that can stabilize intestinal immune homeostasis by maintaining the expression of IL-10 in regulatory B cells [170]. An HFD increased the concentration of serotonin (5-hydroxytryptamine, 5-HT) secreted by colonic chromaffin cells (ECs) [85]. Immune cells carry many 5-HT receptors. High levels of 5-HT under an HFD lead to the abnormal activation of immune cells. For example, 5-HT can pass NF-κB and promote the production of proinflammatory cytokines by dendritic cells [171]. 5-HT can also activate macrophages and increase the expression of NADPH oxidase (NOX) [172], and an increase in NOX activity in macrophages is a significant feature of UC [172].

Seeking dietary intervention strategies for strengthening the gut barrier in UC

Beneficial dietary nutrients

As mentioned earlier, because of its unhealthy dietary ingredients, an HFD can lead to IMB dysfunction by disturbing intestinal microbiota, inducing metabolic changes, affecting programmed death of IECs, reducing intestinal secretion, disrupting intercellular connections, and impairing intestinal immunity. In contrast, some beneficial dietary nutrients can protect IMB function in the HFD environment from the above-mentioned effects. According to the time sequence of dietary nutrients and HFD use, we elaborated its protective effect on IMB based on three dimensions: prevention, inhibition, and recovery. A research study investigated the preventive effect of a blueberry extract called pterostilbene on the susceptibility to HFD-induced colitis. The results showed that pterostilbene could significantly inhibit colitis-associated factors IL-6 and IL-1β and COX-2 expression, reduce the expression of ER stress-associated protein CHOP, maintain the secretion of MUC2, reduce the loss of intercellular connexin E-cadherin, and reduce the expression of colorectal cancer biomarker ACF, thereby reducing the risk of colitis and even colorectal cancer [173]. Another study used apple polysaccharide as an example to explore the effect of dietary nutrients combined with an HFD on the IMB. The results showed that apple polysaccharide supplementation could

increase the abundance of beneficial bacteria such as *Bacteroidetes* and *Lactobacillus*, significantly increase the level of total SCFAs produced by acetic acid and isobutyric acid, upregulate the expression of occludin, and downregulate the expression of TNF-α, MCP-1, chemokine ligand-1 (CXCL-1), and IL-1β, which significantly inhibited HFD-induced damage to the IMB [174]. The effect of supplementation of anthocyanins (ACs) from *Lycium ruthenicum* to the colon after 12 weeks of HFD feeding was investigated. The results showed that ACs could increase the content of SCFA-producing bacteria, reduce the level of LPS-producing bacteria, increase the expression level of intestinal tight junction mRNA and protein, and reduce intestinal inflammation through the LPS/NF-κB/TLR4 pathway [175]. The promotion of intestinal health in the HFD environment by changing nutrients has also been well verified in humans. In a 2-week food exchange trial, African Americans accepted a high-fat and low-fat African diet and rural Africans accepted a high-fat and low-fiber western diet. The results showed that changes in food led to significant interactive changes in intestinal microbiota and metabolomics. For example, after eating low-fat and high fiber, intestinal butyric acid production in African Americans increased, while SBA synthesis decreased [176]. Thus, dietary nutrients can prevent, inhibit, and restore IMB function in an HFD environment to a certain extent.

Beneficial dietary patterns

However, simply increasing dietary nutrient content and reducing fat content does not seem to be a universal formula to protect the IMB. For example, single flaxseed has a protective effect on the IMB [177]; surprisingly, the addition of ground flaxseed to a low-fat diet can exacerbate colitis, which may be due to dietary interactions [178]. The actual dietary intervention pays more attention to the overall dietary patterns than to a single isolated nutrient; hence, it is more important to investigate the role of dietary patterns in the prevention and treatment of UC. A Mediterranean diet (MD) refers to the dietary style of southern European countries along the Mediterranean coast; this diet is dominated by vegetables and fruits, fish, cereals, beans, and olive oil, and it contains less animal fat than a western HFD [179]. A prospective cohort study of 80,000 people showed that adherence to a MD was associated with a lower risk of intestinal inflammation [180]. Recently, three large cohort studies reported that MD compliance is associated with reduced mortality after IBD diagnosis [181]. However, a survey of dietary attitudes found that patients with UC had low compliance with MD [182], which may greatly reduce the therapeutic potential of a MD. Low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet can improve functional gastrointestinal responses such as abdominal distension and abdominal pain; therefore, it is suitable in the treatment of irritable bowel syndrome [183]. However, there are few studies on the treatment of IBD with a low FODMAP diet. A recent randomized, placebo-controlled trial demonstrated that a low FODMAP diet improved intestinal symptoms in patients with resting IBD, but had no effect on inflammatory markers [184]. Moreover, diets with different FODMAP contents had significant effects on the composition of intestinal microbiota [185]. Therefore, more studies are required to clarify the effect of low FODMAP intake on UC. A ketogenic diet (KD) is a high-fat, low carbohydrate diet. This diet could increase the abundance of *Akkermansia* and *Roseburia* and could reduce the production of innate lymphocyte-related proinflammatory cytokines in the colon of group 3, thereby reducing colitis [186]. It is worth noting that although a KD has a high-fat content, it is different from a western HFD; KD is generally dominated by ω3 PUFA and MUFA, while a western HFD is mainly dominated by SFAs and ω6 PUFA. Thus, the type of fat in the diet should also be the focus of dietary intervention. Currently, there is no clinical trial of KD intervention in UC. Because of the physiological differences between animals and humans, clinical research on the effect of KD on UC needs to be conducted urgently.

Beneficial feeding methods

In addition to the changes in dietary patterns, some studies have shown that limited feeding can improve liver metabolism and nutritional utilization of HFD mice without reducing calorie intake [187]. Intermittent fasting was found to improve the metabolism of short-term HFD-fed mice [188]. A research study investigated the effects of alternate-day fasting, time-restricted fasting, and intermittent energy restriction on

intestinal inflammation in mice with UC. The results showed that time-restricted fasting and intermittent energy restriction, rather than alternate-day fasting, could improve colonic microbiota diversity and SCFA production by inhibiting colonic OS and inflammatory response, which improved colonic IMB function and reduced intestinal inflammation [189]. This will be an interesting direction to study whether the limited-time diet combined with a healthy diet model will have a more beneficial effect on the IMB.

There are considerable individual differences in the effects of dietary intervention on intestinal microbiota [190], and the overall structure of intestinal microbiota is mainly affected by long-term dietary intake [191]. Short-term effects are mainly reported in small sample studies [43], which are characterized by extreme and unrealistic dietary intake. Most importantly, there is no universal method. To design the most effective dietary intervention strategy for patients with UC, dietary suggestions must be formulated separately for each patient according to their own disease parameters, so as to achieve the purpose of precise intervention and personalized nutrition. Machine learning seems to be a good approach for this purpose, for example, making dietary plans through machine learning to regulate postprandial blood glucose response has been well received in patients with diabetes [192]. In this regard, we have reason to believe that through appropriate research and sufficient clinical trials, accurate dietary intervention and personalized nutrition will play a very key role in the treatment of UC in the future, which is an attractive prospect.

Conclusion and future perspectives

An HFD damages the IMB in several ways and leads to the occurrence and aggravation of UC. An HFD can affect the structure of intestinal microbiota and the metabolism of FAs, BAs, and TRP, leading to changes in the content of normal substances in the intestinal lumen and damaging the IMB by affecting the programmed death of IECs, inhibiting the secretion of GCs and Paneth cells, damaging intercellular connections, and aggravating the inflammatory response. It is worth noting that because of the various types and additives in an HFD and individual differences between subjects, the metabolic effects of an HFD on the structure of intestinal microbiota and the metabolism of BAs, FAs, and TRP vary; however, in general, an HFD certainly causes a damaging effect on the IMB. In terms of dietary intervention, paying attention to the overall dietary patterns and adjusting the content of dietary nutrients play a positive role in promoting the recovery of barrier function in UC. To achieve precise dietary intervention and personalized nutrition for different UC patients, more research and clinical trials are needed.

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Disclosure of conflict of interest

None.

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