Journal of Translational Gastroenterology **2025** vol. 3(2) | 62–73
DOI: 10.14218/JTG.2024.00038

Review Article

Intestinal Barrier in Inflammatory Bowel Disease: Mechanisms and Treatment

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Received: November 01, 2024 | **Revised:** January 03, 2025 | **Accepted:** March 03, 2025 | **Published online:** May 07, 2025

Abstract

Inflammatory bowel disease (IBD) is an idiopathic intestinal inflammatory condition affecting the ileum, colon, and rectum, including ulcerative colitis and Crohn's disease. Clinical symptoms include abdominal pain, diarrhea, and even bloody stools. The intestinal barrier is the first line of defense between the intestinal tract and the external environment, and maintaining its stability is essential for intestinal health. On one hand, it enables the digestion and absorption of water and nutrients; on the other, it plays a crucial role in reducing the absorption of toxins and the invasion of pathogens. Damage to the intestinal barrier has become one of the most important factors in the onset and progression of IBD. However, there is currently no literature that systematically reviews the mechanisms of the intestinal barrier in the pathogenesis of IBD and the factors influencing it. In this paper, we aimed to systematically elaborate on the role of the intestinal barrier in IBD through the perspectives of oxidative stress, intestinal flora, and cellular autophagy. Our goal was to explore the mechanisms of the intestinal barrier in IBD more deeply and to provide new insights for the diagnosis and treatment of IBD. This article will summarize the composition of the intestinal barrier, the factors affecting it, and strategies to protect it.

Introduction

From the esophagus to the rectum, the entire digestive tract is covered by a mucous membrane. Under homeostatic conditions, the gut and the immune cells in the gut are effective in preventing harmful substances in the gut from entering the circulation and tissues and organs.[1] When intestinal function is impaired, these harmful substances can pass through the intestinal mucosa, triggering an intestinal immune response, which can lead to inflammatory bowel disease (IBD).[2] In this paper, we will discuss the changes in the intestinal barrier during the progression of IBD with the help of domestic and international related studies, with a view to providing new ideas for targeting the intestinal barrier in the treatment of IBD.

Gut barrier composition

The intestinal tract is the organ with the largest contact area with the external environment within the human body. In the gastrointestinal tract, the mucosa constitutes an important barrier—the intestinal barrier. An intact intestinal barrier facilitates nutrient absorption, maintenance of intestinal homeostasis, and defense against disease.[3] Imbalance in intestinal barrier homeostasis is a key component in the development of IBD. The intestinal barrier is mainly composed of mechanical, chemical, immune, and microbial barriers.

Intestinal mechanical barrier

The intestinal mechanical barrier consists of intestinal epithelial cells (IECs), intestinal mucus, and tight junctions with neighboring IECs. It is the foundation of the intestinal mucosal barrier. IECs, which mainly include goblet cells, Paneth cells, and M cells, are the pillars of the intestinal mechanical barrier and play a central role in the host's intestinal defense.[4] Intestinal epithelial cells not only have the ability to rapidly proliferate and regenerate, but also secrete intestinal mucus, antimicrobial peptides (AMPs), and secretory immunoglobulin A (SIgA), which are the structural basis for the maintenance of the intestinal chemical barrier, immune barrier, and other barrier functions.[5] In particular, intestinal mucus—a highly glycosylated mucin secreted by goblet cells—is an important component of the physical barrier of the intestine. It covers the surface of intestinal epithelial cells and acts as a physical barrier, preventing the gut microbiome from acting directly on the intestinal mucosa.[6] Connections between neighboring epithelial cells in

Keywords: Inflammatory bowel disease; Colitis; Intestinal barrier; Oxidative stress; Intestinal flora; Autophagy.

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How to cite this article: Zhao Z, Liu X, Zhang R, Ke R, Zhang S, Chen Y. Intestinal Barrier in Inflammatory Bowel Disease: Mechanisms and Treatment. *J Transl Gastroenterol* 2025;3(2):62–73. doi: 10.14218/JTG.2024.00038.

the intestine constitute the junctional complexes, which include, in order: tight junctions, gap junctions, adherens junctions, and desmosomes.[7] As a key part of the physical barrier, tight junctions are mainly composed of claudins, occludin, junctional adhesion molecules, and zonula occludens-1 (ZO-1), which maintain the structural stability between epithelial cells in the intestinal mucosa. Once the physical barrier is damaged, the residual stem cells located at the base of the crypt will be stimulated to differentiate into mature epithelial cells to repair the damaged mucosa.[7] Clinical studies have found that downregulation of the expression of relevant proteins such as occludin and ZO-1 can be observed in patients with ulcerative colitis (UC).[8] Animal studies have shown that dextran sodium sulfate (DSS) induces intestinal inflammation and barrier damage in mice, which triggers the invasion of harmful substances into the intestinal epithelium and lamina propria, causing intestinal mucosal damage.[9] Thus, it appears that intact tight junctions play an important role in maintaining the normal function of the intestinal mechanical barrier.

Intestinal chemical barrier

The intestinal chemical barrier consists of mucus, mucin, water, digestive enzymes, AMPs, mucin 2 (Muc2), and other substances, also known as the mucus layer, which is located between the intestinal epithelium and the intestinal microbial layer.[10] The Muc2 mucus barrier allows small nutrient molecules (e.g., ions and other compounds) to be absorbed normally by the intestinal epithelium, whereas harmful substances, such as bacteria, are effectively blocked by the Muc2 mucus barrier.[9] Reduced Muc2 can lead to decreased chemical barrier integrity, and studies have demonstrated that genetically deficient mice with knockout of Muc2 progressively develop intestinal barrier damage and UC symptoms as they grow.[11] AMPs are produced by intestinal epithelial cells and include α-defensins, β-defensins, RegIIIγ, and C-type lectins. AMPs are involved in the early stages of the host's immune response to pathogens, acting through epithelial and immune cells to inhibit pathogen invasion. LL-37 is a human host AMP that induces vitamin D3 butyrate to promote host immune function by enhancing the expression of endogenous LL-37 and its mediated cGAMP immune response.[12] LL-37 can be detected in the intestinal mucosa of patients with UC, and compared to healthy controls, patients with UC have significantly higher serum LL-37 levels. Moreover, the intestinal mucosa of patients in the high LL-37 level group also showed a trend toward better recovery.

Intestinal immune barrier

The intestinal immune barrier consists of the innate immune system (IIS) and the adaptive immune system. The innate immune system includes elements such as myeloid cells, mucins, and AMPs, and the IIS expresses pattern recognition receptors such as toll-like receptor 4 (TLR4) and Nod-like receptors (NLRs), which allow it to distinguish between pathogen-associated molecular patterns and damage-associated molecular patterns. Damage-associated molecular patterns and pathogen-associated molecular patterns activate the IIS by interacting with pattern recognition receptors.[13] These patterns can be sensed by granulocytes, neutrophils, monocytes, myeloid-derived suppressor cells, macrophages, and dendritic cells that comprise the IIS. In addition, the IIS responds to anti-inflammatory signals released by these cells by temporarily strengthening the intestinal epithelial barrier and clearing inflammation.[14]

Adaptive immunity consists mainly of gut-associated lymphoid tissue (GALT) and SIgA,[15] where GALT includes Peyer's patches (PPs) and isolated lymphoid follicles. As the largest lymphoid tissue in the body, GALT can uptake, process, and present antigens to promptly recognize foreign and abnormal antigens. After specifically recognizing foreign antigens, GALT promotes the production of cytokines and antibodies to complement the immune response. In addition, it activates T and B lymphocytes to establish an effective adaptive immune response and induce mucosal immune response or immune tolerance[16] with PPs considered a key site of the intestinal immune response in both humans and mice. A single-center study has shown altered PP morphology detected by narrow-band imaging in people with recurrence of UC, and observation of PP morphology may assist in clinical diagnosis.[17,18] SIgA, secreted by B cells in the lamina propria of the mucosa, is one of the most abundant immunoglobulin isoforms in the intestinal mucosa and the first line of intestinal immune defense.[17] It has been found that promoting SIgA in the gut can stimulate the secretion of intestinal mucus and interact with commensal bacteria. It prevents bacteria from adhering to the intestinal mucosa, protects the intestinal tract from damage by foreign antigens, and avoids activation of abnormal immune responses.[19] It also regulates the function of the intestinal mucosal immune barrier, increases pathogen resistance, and promotes the restoration of intestinal homeostasis. The disruption of the intestinal immune barrier is one of the important pathogenetic features of IBD. Normal intestinal immunity can resist pathogen invasion, but persistent abnormal immune responses can damage the intestinal mucosal barrier, thereby exacerbating the development of IBD.

Intestinal microbial barrier

The microbial barrier is composed of intestinal flora, which mainly includes Anaplasma phylum, Aspergillus phylum, Actinobacteria phylum, and Thick-walled bacteria phylum.[20] Intestinal flora can form a bacterial membrane, creating a line of defense with epithelial cell tight junctions and assisting the intestinal mechanical barrier in resisting the invasion of foreign pathogenic bacteria. Additionally, it can resist foreign bacteria through its metabolites (e.g., butyrate, bile acids, etc.) and function as a chemical barrier together with the mucus secreted by Paneth cells.[21] Dysbiosis of the gut microbiota is one of the important factors contributing to the development of IBD. The microbiota can be categorized into probiotics, pathogenic bacteria, and opportunistic pathogens. Probiotics are the dominant intestinal bacteria, including Lactobacillus spp. and Bifidobacterium spp. Pathogenic bacteria are relatively few anaerobic bacteria, mainly including Clostridium tetani, Staphylococcus spp., and so on. Opportunistic pathogens include some enterococci, which are harmless under normal circumstances but can cause damage to the body under certain conditions.[22] The development of inflammatory bowel disease may be related to the involvement of intestinal flora in immune regulation. Intestinal flora can regulate the balance of Treg and T helper type 17 (Th17) cells in the intestinal mucosa, and IL-17A, IL-17F, and IL-22 secreted by Th17 cells can ensure the normal functioning of the immune system.[23] In summary, the gut microbial barrier plays a crucial role in the pathogenesis of IBD.

Factors influencing the intestinal barrier

Intestinal barrier function is affected by many factors, including the occurrence of oxidative stress, changes in intestinal flora, autophagy, environmental pollution, obesity, and drugs. The maintenance of intestinal health requires a comprehensive consideration of these factors. The following will discuss the impact of these factors on the intestinal barrier in the occurrence and development of IBD, so as to find different treatment modalities.

Oxidative stress causes IBD by damaging the intestinal barrier

Among the immunomodulatory pathways, oxidative stress has been proposed as one of the main mechanisms involved in the pathophysiology of IBD. Oxidative stress refers to the phenomenon of excessive production of reactive oxygen species (ROS) resulting from an imbalance between oxidative and antioxidant effects in the body, which triggers cellular and tissue damage,[24] and under normal physiological conditions, the rate of ROS production and the rate of antioxidant scavenging by the body constitute the oxidative-antioxidant homeostatic system of the organism.[25] However, intestinal inflammation in IBD is usually accompanied by excessive production of ROS. High levels of ROS lead to enhanced cellular oxidative stress, an imbalance in the body's oxidative-antioxidant system, damage to the intestinal mucosal layer, and apoptosis of epithelial cells, leading to bacterial invasion in the gut and stimulation of immune responses and tissue damage.[26] It has been established that chronic intestinal inflammation is closely related to the overproduction of ROS and reactive nitrogen species.[27]

Mitochondrial oxidative stress in IBD

Mitochondrial oxidative stress plays a crucial role in maintaining the intestinal epithelial barrier during inflammation,[28] and mitochondria are the main source of intracellular ROS. In IBD, the overproduction of mitochondrial ROS leads to damage and dysfunction of cell membranes, exacerbating inflammatory responses in IBD and further causing tissue damage.[29] Diarrhea is one of the hallmark symptoms of patients with IBD, which is often accompanied by mucous and bloody stools, and previous studies have suggested that ROS can stimulate the production of inflammatory factors, leading to intestinal flora dysbiosis through signaling pathways such as nuclear factor kappa-B (NF-κB).[30] In addition, Wilson *et al*.[31] found that oxidative stress disrupts tight junction proteins, which in turn leads to the passive diffusion of water and ions from the intestinal mucosa into the intestinal lumen and the development of diarrhea. The reason for this may be due to the fact that in the presence of mucosal inflammation, inflammatory cytokines activate NADPH oxidase (NOX) and inducible NO synthase (iNOS), leading to the production of superoxide and nitric oxide by IECs, neutrophils, and macrophages. IECs produce more ROS/reactive nitrogen species by activating NOX and iNOS. The presence of excess ROS has the potential to cause damage to cytoskeletal proteins, leading to disruption of intestinal tight junctions and increased intestinal permeability, which can exacerbate IBD and lead to diarrhea.[32]

Inhibition of oxidative stress by the Kelch-like ECH-associated protein 1 (Keap1)/Nrf2 pathway

An imbalance between oxidative and antioxidant systems can promote the activation of oxidative stress-related pathways that mediate intestinal tight junction destruction, apoptosis, and necrosis. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcriptional regulator molecule involved in redox homeostasis and plays a critical role in promoting antioxidant responses in organisms.[33] The Keap1/Nrf2 signaling pathway consists of the major regulator Nrf2 and its trans-acting inhibitor Keap1. This signaling pathway has been shown to exert protective effects in animal models and in individuals with UC. In the cytoplasm, Keap1 protein normally binds to Nrf2 to stabilize Nrf2 in the cytoplasm. Upon oxidative stress in the cell, the Nrf2-binding domain of the Keap1 protein is modified to release Nrf2, which can then be translocated into the nucleus and bind to AREs and activate antioxidant responses through upregulation of the expression of downstream target genes, including Nqo1, Hmox1, and Sod1, to reduce intracellular ROS production and attenuate cytotoxicity from oxidative stress, reducing tight junction destruction and thereby ameliorating DSS-induced colitis. In this regard, the Keap1/Nrf2 signaling pathway is crucial as an antioxidant defense mechanism.[34] In a study on mice, researchers used Rutaecarpine (RUT) to significantly reduce DSS-induced IBD in mice. Mechanistically, RUT interfered with Keap1-Nrf2 interactions to induce nuclear Nrf2 translocation, which then activated downstream antioxidant protective responses to ensure IEC and tight junction integrity (Fig. 1). The new study shows that the targeted regulation of the Keap1/Nrf2 protein also becomes one of the ways to regulate oxidative stress.[35] An miRNA is a small non-coding RNA sequence containing about 22–24 nucleotides. They inhibit gene expression by binding to complementary sequences in the 3′-untranslated region (UTR) of target mRNA and regulate many biological functions. miR-941, a novel miRNA targeting Keap1, protects cells from oxidative stress by inhibiting Keap1 3′-UTR expression, thus activating the Nrf2 cascade.[36] These results demonstrate that the Keap1/Nrf2 pathway offers a novel option for the treatment of clinical IBD by protecting the intestinal barrier.[37]

Intestinal flora

The intestinal flora is established from the time of human birth and evolves to form a stable microecological barrier system, i.e., the intestinal microbial barrier. The intestinal flora can participate in the body's metabolism, promote the maturation of the immune system, and protect the intestinal nerves. However, when the intestinal physical and chemical barriers are damaged, the intestinal flora can penetrate the intestinal barrier into the lamina propria and induce abnormal immune responses. The Muc2 mucus barrier is the first barrier preventing direct contact between intestinal bacteria and colonic epithelial cells,[11] and Muc2 mutant mice can inhibit intestinal cuprocyte endoplasmic reticulum stress, which causes a decrease in mucus secretion and an increase in protein misfolding. Under aseptic conditions, this can cause mild spontaneous colitis in the absence of bacteria and severe and persistent colitis in the presence of intestinal flora.[38] Another feature of the intestinal flora of IBD patients is the generalized decrease in abundance or absence of bacteria such as Faecalibacterium prausnitzii and Roseburia.[39] As short-chain fatty acid (SCFA)-producing bacteria, normal abundance of Faecalibacterium prausnitzii and Roseburia promotes intestinal epithelial growth, mucus secretion, and immunomodulation.[39] In conclusion, the total amount and diversity of flora in the gut are reduced in IBD patients. In addition, gut flora metabolites, including butyrate, bile acids, and lipopolysaccharide (LPS), contribute to the development of IBD.[40]

Butyrate affects intestinal barrier mechanisms

Butyrate is produced via the acetyl coenzyme A, lysine, glutarate, or succinate pathways in colonic tissues, and the reduced levels of butyrate in patients with active UC, along with the restoration of butyrate levels in the feces of patients with remission-phase UC, suggest that butyrate plays an important role in the pathogenesis of UC.[41] Among microbial metabolites, butyrate may modulate the intestinal barrier through the following mechanisms: (i) Regulation of the chemical barrier: Butyrate can increase the expression of Muc2 and SPDEF genes in cuprocytes via M2-type macrophages, and the secretion of butyrate to cuprocyte Muc2 can be significantly reduced when the WNT/RAS-extracellular signal-regulated kinase (ERK) signal in M2 macrophages is blocked. Therefore, butyrate promotes the repair of the intestinal mucus barrier through activation of the M2/WNT/ERK signaling pathway.[41] (ii) Regula-

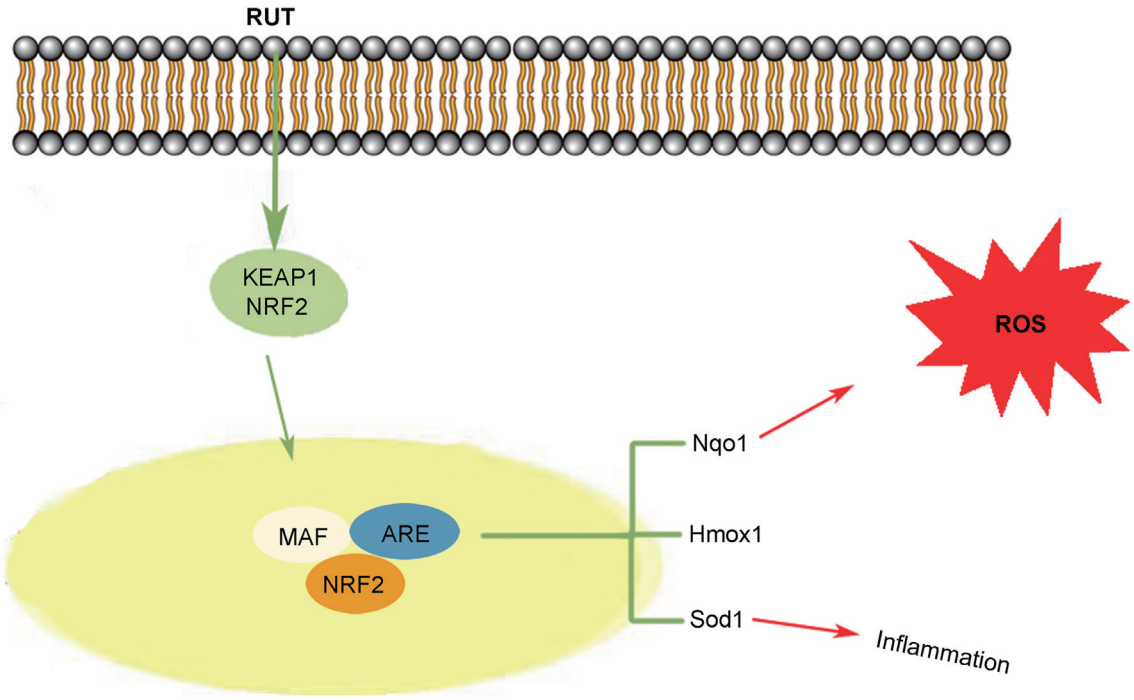

Fig. 1. RUT inhibits the molecular pathway of DSS-induced IBD in mice, created with BioRender.com. RUT, rutabaecarpine; KEAP1, Kelch-like ECH-associated protein 1; NRF2, Nuclear respiratory factor 2; MAF, MAF translation factor; ARE, Antioxidant response element; NRF2, Nuclearfactor erythroidderived 2-like 2; Nqo1, NAD(P)H quinone oxidoreductase 1; Hmox 1, Heme Oxygenase 1; Sod1, Superoxide Dismutase; ROS, Reactive oxygen species.

tion of the mechanical barrier: It was found that butyrate enhances intestinal barrier function by activating AMP-activated protein kinase (AMPK), protein kinase B (PKB), and other signaling pathways in a dose-dependent manner to promote tight junction assembly. Wang *et al*.[42] demonstrated that butyrate treatment upregulates the claudin-1 promoter region by promoting interactions between specific motifs in the promoter region and SP1 transcription factors, which upregulates claudin-1 transcription, thereby improving epithelial barrier function. (iii) Regulation of the immune barrier: Butyrate regulates the differentiation and proliferation of T cells. Treg cells have immunosuppressive properties and help maintain immune homeostasis through the secretion of anti-inflammatory cytokines, including interleukin-10 (IL-10),[43] and T helper type 17 (Th17) cells produce inflammatory cytokines, such as interleukin-17A (IL-17A), interleukin-17F (IL-17F), and interleukin-21 (IL-21), which are involved in the pathogenesis of IBD. The gut microbial metabolite butyrate regulates T cell differentiation and proliferation. Butyrate administration enhanced Treg cell function, inhibited IL-17 levels and Th17 cells in peripheral blood and colonic tissues, and reduced the secretion of pro-inflammatory factors, such as IL-17A, IL-17F, and IL-21, in rats with TNBS-induced colitis, compared to the control group (Fig. 2).[44]

Bile acids influence the intestinal barrier mechanism

Bile acids are synthesized by the liver from cholesterol and subsequently converted to secondary bile acids for action by the intestinal flora. Bile acids interact with bile acid receptors and the intestinal microbiota and play a key role in maintaining the homeostasis of the intestinal mucosal barrier. Studies have shown that bile acids can alter intestinal mucosal permeability and influence the intestinal barrier by regulating the expression of tight junction proteins. Primary bile acids are metabolized by intestinal flora to secondary bile acids, deoxycholic acid, and lithocholic acid (LCA),[45] which have been shown to improve the distribution of TNF-α-induced tight junction proteins ZO-1, E-cadherin, occludin, and claudin-1. LCA has a significant protective effect on TNF-α-induced intestinal barrier function damage through the vitamin D receptor (VDR). Inhibition of NF-κB signaling and activation of the SIRT1/Nrf2 pathway may be one of the potential mechanisms for the protective effect of LCA.[46] The administration of curcumin, a polyphenolic compound isolated from turmeric, reduced LPS-induced intestinal tight junction injury and attenuated acute inflammation of the mucosa, possibly by altering the microbiome and modulating bile acid metabolism.[47]

LPS affects intestinal barrier mechanisms

LPS, also known as endotoxin, is a component of the outer cell wall of Gram-negative bacteria.[48] LPS of intestinal microbial origin can disrupt the intestinal barrier by inducing inflammation and reducing occludin and claudin-1, the essential components of the tight junction.[49] In addition, LPS can damage the intestinal barrier through the TLR4/NF-κB signaling pathway. After activation of the TLR4 receptor on the membrane of the intestinal epithelial cells by LPS, it promotes the downstream phosphorylation of the IkappaBa and p65 proteins, inducing the IkappaBa degradation after p65 ectopic to the nucleus. Ultimately, LPS leads to tight junction injury through the TLR4/NF-κB pro-inflammatory pathway, which in turn aggravates the development of IBD.[49]

In summary, the levels of butyrate, bile acids, and LPS, which are metabolites of the intestinal flora, play an important role in the pathogenesis and treatment of IBD. Maintaining gut microbial homeostasis and reducing microbial-derived LPS secretion through dietary therapy or supplementation with butyrate and bile acids may be one of the important targets for future IBD treatment.

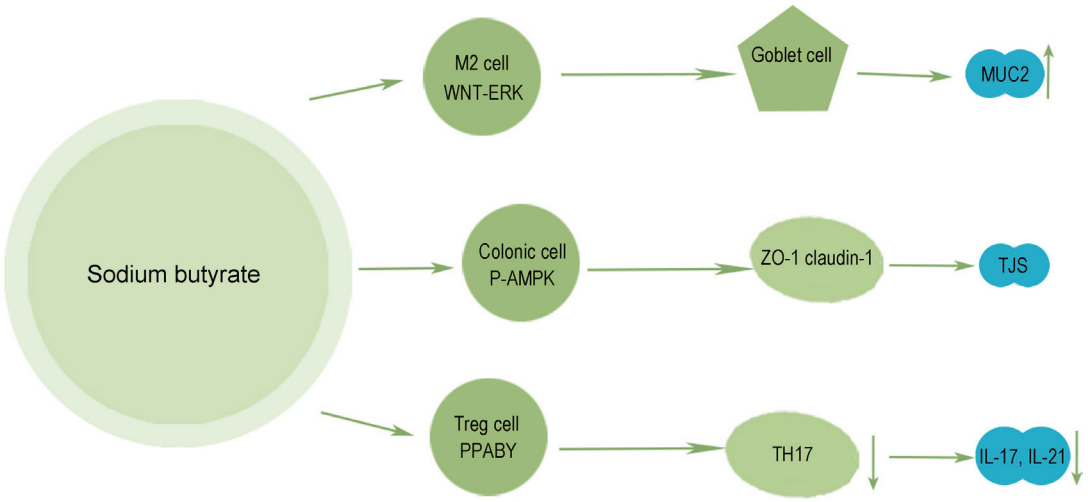

Fig. 2. Protection of intestinal barrier by sodium butyrate,ametabolite of intestinal microbes. Wnt, Wnt protein; ERK, extracellular regulated protein kinases; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; ZO-1, zonula occludens-1; TH17, T helper cell 17; MUC2, mucoprotein2; TJ, tight junction; IL-17, interleukin 17; IL-21, interleukin 21; ↓, The amount of this substance secreted by cells increases; ↑, The amount of this substance secreted by cells decreases.

Cellular autophagy and the intestinal barrier

Autophagy is a catabolic cellular process in which a number of protein aggregates and damaged organelles are degraded into metabolic components for recycling via lysosomes to maintain cellular homeostasis and viability.[50] Autophagy is mainly classified into three classical forms, including macroautophagy, microautophagy, and molecular chaperone-mediated autophagy.[51] The main function of macroautophagy is to recycle and reabsorb nutrients from the cytoplasm under metabolic stress conditions and to degrade specific cytoplasmic components.[51,52] Microautophagy is a non-selective form of autophagy that engulfs cytoplasmically degraded material through lysosomal/vesicular membrane invaginations.[53] Chaperone-mediated autophagy is a selective form of autophagy that relies on the presentation of chaperones via substrate proteins and certain target motifs in lysosomal chaperones.[54]

During autophagy in enterocytes, autophagy-related proteins, autophagy-related protein 16-like 1 (ATG16L1), immunity-related GTPase M (IRGM), and autophagy-associated proteins are the most important proteins involved in autophagy,[55] and autophagy may be involved in protecting the intestinal mucosal barrier, possibly through the removal of cells, the mechanism of which may regulate the intestinal mucosal barrier by removing intracellular bacteria. Studies have shown that infection of mice defective in the autophagy-related gene ATG16L1 and normal mice using Salmonella typhimurium revealed increased autophagy-related protein LC3 in the small intestinal epithelial cells of the normal mice, but not in the ATG16L1-deficient mice, as well as heavier inflammation and intestinal bacterial translocation than in normal mice. It has been shown that ATG16L1 expression regulates autophagy in intestinal epithelial cells, preventing intestinal barrier damage caused by intestinal bacterial translocation, which can lead to infection.[56] Whereas defective autophagy affects cellular clearance of invading pathogens, knockdown of ATG16L1 significantly reduces the formation of autophagic vesicles containing bacteria, and the inhibition of autophagy in intestinal epithelial cells leads to dysfunction of autophagic clearance of intracellular bacteria, causing inflammation to occur.[57]

Inflammatory vesicles in cellular autophagy

Inflammatory vesicles are considered to be a type of multiprotein oligomer responsible for the activation of the inflammatory response.[58] They belong to the innate immune family and are mainly found in most inflammatory and immune cells in the epithelium and gut, such as macrophages and dendritic cells. The NLRP3 inflammasome is composed of three components, including NLRP3 protein, apoptosis-associated spot-like protein, and procaspase-1.[59] It has been found that autophagy can cause the activation of inflammatory vesicles and excessive inflammatory response. Under inflammatory conditions, NLRP3 inflammatory vesicles bind and promote mechanistic target of rapamycin (mTOR) phosphorylation, inhibit autophagy, and disrupt autophagy-mediated elimination of pro-inflammatory mediators, thus exacerbating inflammation.[60] In a mouse model of DSS-induced colitis, hypoxia inhibits intestinal inflammation by down-regulating NLRP3-mTOR binding, thereby activating autophagy-mediated degradation of NF-κB signaling mediators and decreasing the expression of pro-inflammatory genes.[61] In response to intracellular pathogens, caspase-4 is activated, leading to activation of inflammatory vesicles, which positively regulates macrophage autophagic vesicle biogenesis and translocation to lysosomes, increasing heterophagy-mediated elimination of pathogens.[61] The above evidence suggests that overactivation of the NLRP3 inflammasome leads to excessive inflammatory response and intestinal damage in the gut. Inhibition of the overactivation of NLRP3 inflammatory vesicles can alleviate colitis, and in one study, triggering of the cholinergic anti-inflammatory pathway by administration of the alpha7 nicotinic acetylcholine receptor agonist PNU282987 was found to alleviate DSS-induced colitis. The alleviation process is mediated by inhibition of the NLRP3 inflammatory vesicle-associated AMPK-mTOR-p70S6K signaling pathway, which reduces IL-1β and IL-18 production (Fig. 3).[62]

Mitochondrial autophagy in inflammatory bowel disease

Mitochondrial autophagy is closely related to IBD. Normal mitochondria can activate the apoptotic pathway by releasing pro-apoptotic proteins and removing senescent or dysfunctional mito-

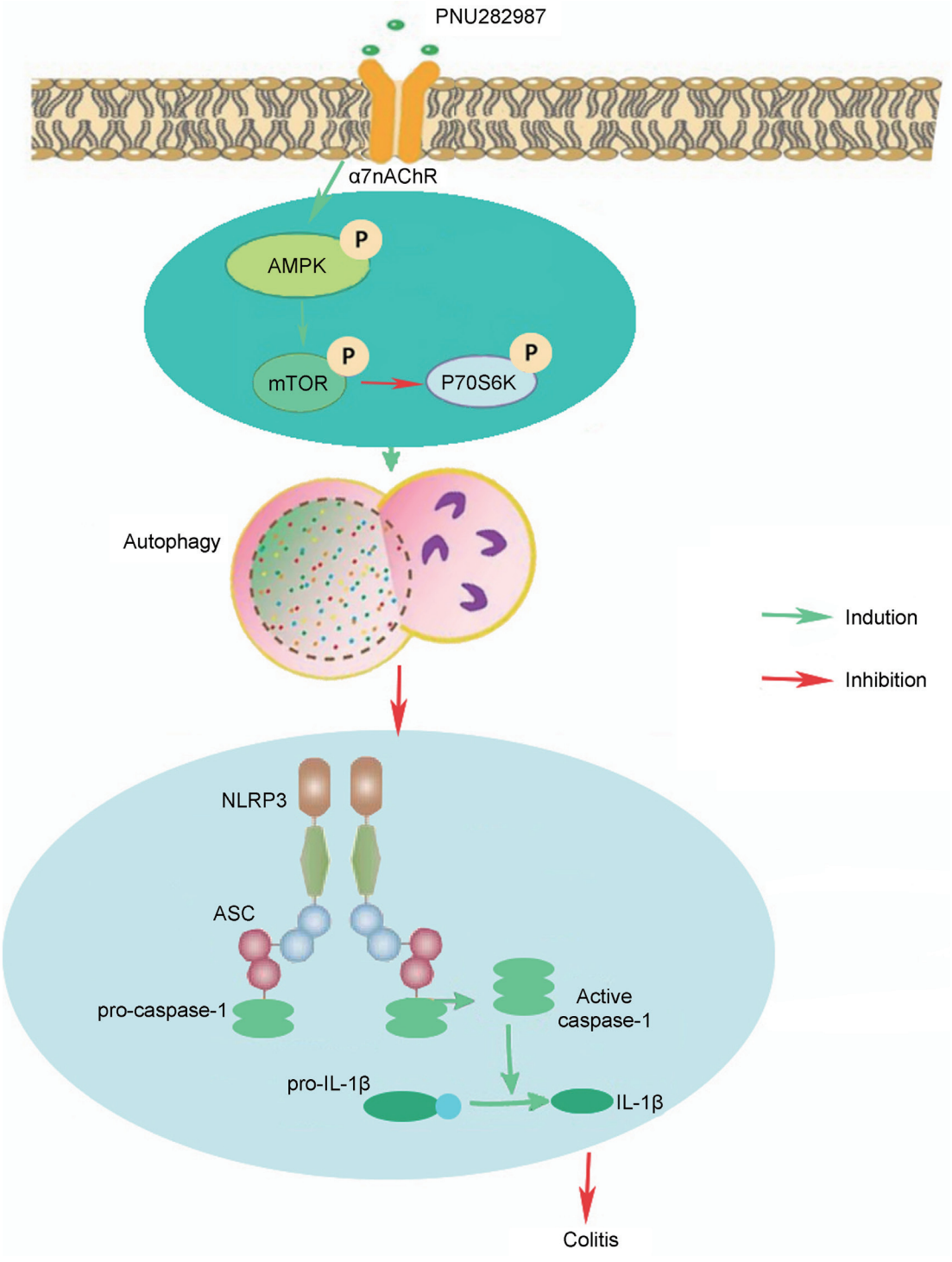

Fig. 3. PNU282987 alleviates the DSS induced colitis signaling pathway through cholinergic anti-inflammatory pathway, created with BioRender.com. mTOR, mammalian target of rapamycin; p70S6K, The 70kDa ribosomal S6 kinase 1; NLRP3, NOD-like receptor thermal protein domain associated protein 3; ASC, apoptosis-associated speck-like protein containing a CARD; caspase, cysteinyl aspartate specific proteinase; IL-1β, Interleukin-1beta.

chondria. The normal function of intestinal epithelial cells requires healthy mitochondria to provide sufficient energy, and dysregulated mitochondrial autophagy in intestinal epithelial cells leads to intestinal mucosal barrier dysfunction, which in turn leads to severe oxidative stress and intestinal inflammation.[63] It has been demonstrated that the intestinal mucosa of IBD patients is in an energy-deficient state, i.e., low ATP levels and low-energy potentials. IRGM1 and ATG16L1 are key molecules in the mitochon-

drial autophagy mechanism, and knockdown of the IRGM gene in mitochondria in DSS-induced colitis mice leads to a reduction of Paneth cells in colon samples of colitis mice, abnormal mitochondrial elongation and division, and ultimately leads to autophagy dysfunction. Knockdown of the ATG16L1 gene leads to increased mitochondrial swelling and transparency, accompanied by increased ROS levels in mouse colon samples.[64] It has been shown that knockout of IRGM/Irgm1 and ATG16L1 genes leads to abnormal mitochondrial autophagy function, which prevents cells from efficiently removing damaged or aged mitochondria. This situation further causes increased ROS production, which damages the intestinal barrier through the oxidative stress pathway, leading to the development of IBD.[56]

Macrophage autophagy in inflammatory bowel disease

The gut has the largest macrophage population of any organ, and intestinal macrophages can protect the gut from invasion and damage by phagocytosis and presentation of invading antigens to other immune cells.[65] Polymorphisms in ATG16L1, NOD2, and IRGM are present in the macrophages of patients with Crohn's disease (CD), leading to defects in macrophage autophagy, which has been shown to be one of the etiological factors of CD.[66] Mutations in ATG16L1, NOD2, or IRGM can all lead to the inability of macrophages in the intestines of CD patients to restrict the colonization of adherent invasive Escherichia coli (AIEC), leading to the disruption of the intestinal barrier, which in turn contributes to the development of CD. AIEC can lead to reduced ZO-1 expression and increased cellular gaps, suggesting that intercellular integrity is compromised, indicating the disruption of intact intercellular tight junctions.[67] In addition, AIEC can indirectly inhibit the expression of Junctional Adhesion Molecule A through the release of inflammatory factors (e.g., TNF-α, IL-6) by infected macrophages, leading to disruption of the integrity of the tight junction complexes, impairing the mechanical barrier of the intestinal mucosa, and further promoting the development of IBD.[67]

The role of cellular autophagy in the development of IBD is now recognized. Cellular autophagy participates in the inflammatory process through certain signaling pathways, exerting inhibition of inflammatory factors and promotion of anti-inflammatory factors to reduce intestinal damage and protect the intestinal mucosal barrier. Abnormalities of autophagy in inflammatory vesicles, mitochondria, and macrophages can stimulate intestinal barrier damage and lead to intestinal inflammation.

Other factors that can lead to inflammatory bowel disease

Impact of pollutants on the intestinal barrier

New research has found that pollutants also play a crucial role in compromising barriers in IBD.[68] Bisphenol A (BPA) is one of the most commonly used industrial compounds, mainly used in the production of epoxy resins and polycarbonate materials.[69] A large number of studies have reported a variety of adverse effects of BPA, including developmental disorders, reproductive toxicity, and cardiovascular toxicity. There is increasing evidence that bisphenol can enter the gastrointestinal tract. Zhu *et al*.[70] found that BPA exhibited downregulation of the expression of key genes responsible for intestinal homeostasis and cell proliferation in the crypts at high doses (5 mg/kg/d). Importantly, BPA inhibited cell differentiation, increased mucin levels, and downregulated the expression of tight junction markers, resulting in damage to the chemical and physical barriers of the gut.[69]

Impact of obesity on the intestinal barrier

Faulty dietary habits are also closely related to the development of IBD,[71] and recent evidence suggests that a high-fat diet leads to intestinal hyperpermeability and damage to the intestinal physical barrier through the LPS turnover mechanism.[72] LPS can cause intestinal hyperpermeability through the direct regulation of tight junction tissues, TLR4-Cluster of Differentiation 14-mediated activation of NF-κB, and induces IEC dysfunction, which causes intestinal hyperpermeability.[73] LPS can also be incorporated into chylomicron particles, which transport dietary lipids from the intestine via lipid A tails and distribute them into the bloodstream, causing a systemic inflammatory response.[74] Obesity due to a high-fat diet can also alter the gut microbiota, changing the relative proportions of the Mycobacterium anisopliae phylum, Mycobacterium thickum, and Actinobacterium phylum in obese populations compared to lean control populations.[75] A similar study in obese children aged six to sixteen years also showed elevated ratios of phylum Thick-walled to phylum Actinobacteria compared to lean children, with lower relative proportions of unusual Actinobacteria and higher concentrations of Lactobacillus spp. observed in the obese population.[76] The relative abundance of several other specific bacterial groups appears to be enhanced in obese individuals, including Lactobacillus, Staphylococcus aureus, and Escherichia coli.[77] Studies have shown that these physical and functional components of the intestinal barrier are altered in obese individuals; therefore, it is plausible that the gut and/or intestinal barrier may contribute to the systemic inflammation associated with obesity.

Effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the intestinal barrier

NSAIDs, mainly including aspirin, ibuprofen, celecoxib, and parecoxib, are widely used in the treatment of pain and inflammation caused by various diseases such as rheumatoid arthritis and osteoarthritis. NSAIDs act by inhibiting the synthesis of cyclooxygenase (COX) and thus prostaglandins.[78] The main adverse effects of NSAIDs on the gastrointestinal tract are ulceration and intestinal perforation, which may be caused by altering the distribution of intestinal microorganisms.[79] Although one report states that a single oral dose of indomethacin does not cause damage to the small intestine, but instead induces adaptive changes in gut microbes, including the abundance of the phylum Thick-walled and Mycobacterium spp,[80] systemic administration of indomethacin leads to the development of intestinal inflammation characterized by intestinal TLR4 receptors as well as the abundance of Anabaena spp. and Enterobacter spp. in the rat ileum.[81] Chlorogenic acid, a naturally occurring bioactive polyphenol with anti-inflammatory, antioxidant, and antimicrobial effects, has been shown experimentally to be effective in indomethacin-induced colitis, mainly through inhibition of Anabaena spp. and the accumulation of Mycobacterium avium-derived LPS, thereby alleviating indomethacin-induced intestinal damage.[81]

Intestinal barrier-related therapy

Traditional IBD therapeutic drugs (e.g., aminosalicylic acid preparations, glucocorticoids, etc.) have been widely used in clinical practice. However, with advances in research on the mechanisms of IBD, traditional treatments can no longer meet the needs of patients. Emerging treatments, such as fecal microbiota transplantation (FMT) and electroacupuncture (EA) therapy, have also been shown to be therapeutic for IBD. The following section focuses on how these therapeutic modalities act on the intestinal barrier and treat IBD.

Conventional drug therapy

Mesalazine, also known as 5-aminosalicylic acid, not only inhibits the synthesis of prostaglandins and leukotrienes, which induce intestinal inflammation, but also significantly increases the expression of tight junction proteins, such as JAM-A and occludin, in colonic tissues, helping to restore the intestinal mechanical barrier. In addition, intestinal 5-aminosalicylic acid in the intrinsic gut flora blocks the growth of pro-inflammatory bacteria, such as Shigella escherichiae, and increases the number of Escherichia coli, which plays an important role in maintaining the intestinal microbial barrier.[82] Glucocorticoids also play an important role in maintaining intestinal epithelial integrity. TNF-α induces the expression of tumor necrosis factor receptor 2 on IECs, which subsequently binds to tumor necrosis factor receptor 2 and activates myosin light chain kinase, increasing epithelial permeability during inflammation.[83] However, glucocorticoids can bind to the glucocorticoid receptor complex on the IEC and inhibit the TNFα-induced increase in myosin light chain kinase activity, reducing tight junction injury and protecting the intestinal epithelial barrier.[84,85]

FMT to repair the intestinal barrier in IBD

FMT refers to the transplantation of functional bacteria from healthy donors into the intestines of IBD patients to restore or reestablish intestinal flora homeostasis.[86] A single-center prospective cohort study of 122 patients with UC showed that patients who received FMT and glucocorticoid therapy achieved an equivalent therapeutic effect. However, FMT reduced serum levels of TNF-α and IL-6 and was associated with fewer adverse events compared to glucocorticoid therapy.[87] Colon transendoscopic enteral tubing (TET) is an FMT method that allows for endoscopic-guided insertion of a thin flexible tube through the anus into the deep colon, where it is fixed at a specific location for drug delivery, allowing for total colonic coverage. Compared with other methods, colonic TET drug delivery is safer, more effective, and has higher patient satisfaction.[88] Wen *et al*.[89] found that FMT restored chemically induced intestinal flora imbalance, upregulated lactobacilli abundance, maintained intestinal microbial barrier homeostasis, and ameliorated colitis in chemically induced mice. Therefore, receiving FMT can alleviate the clinical symptoms of patients, especially with colonic TET administration. However, whether FMT subsequently causes serious adverse events has not been systematically studied,[89] and this remains a matter of discussion.

EA to repair the intestinal barrier in IBD

Acupuncture is a traditional Chinese medical therapy, and EA is a method of treating diseases by outputting pulsed current through an electroacupuncture instrument and acting on acupuncture points.[90] EA has now been shown to be therapeutic for IBD in clinical trials. The Foot Sanli (ST36) acupoint is commonly used for EA treatment. EA at ST36 can protect the intestinal epithelial barrier through multiple pathways. The Notch signaling pathway consists of Notch receptors, ligands, and CSL proteins.[91] Notch signaling inhibits secretory cuprocytosis by activating the Hes-family bHLH transcription factor 1, thereby decreasing Muc2 secretion. EA inhibits secretory cuprocytosis, thus reducing Muc2 secretion. EA at ST36 inhibits this pathway and increases the amount of Muc2 secreted by goblet cells, thereby repairing the intestinal chemical barrier.[92] In addition, EA at ST36 increased the levels of ZO-1, Occludin, and Claudin-1 in the intestinal epithelial cells of UC colon tissues, restored the number of enterocyte tight junctions, and repaired the intestinal mechanical barrier.[93] New studies have also shown that EA at the Tianshu acupoint (ST25) improved the colonic status of DSS-induced acute UC rats. The mechanism may involve the activation of AMPK and inhibition of mTOR phosphorylation through the phosphorylation of tuberous sclerosis protein complex and Raptor proteins, which improves the level of intestinal autophagy and alleviates colonic inflammation.[94]

Vitamin supplementation therapy to repair the IBD intestinal barrier

Vitamins are micronutrients that humans and animals must obtain from food, and they are crucial for maintaining a healthy intestinal microbiota, promoting growth and development, metabolism, and innate immunity. There is a close link between vitamin deficiency, intestinal flora dysbiosis, and IBD.[95] Current research has found that vitamin A (VA) can maintain the natural barrier function of gastrointestinal mucosal epithelial cells, regulate mucosal immune responses and intestinal flora, and support the normal immune function of the intestinal tract.[96] VA is also involved in the pathological process of many diseases related to intestinal barrier function, and supplementation of VA can improve the intestinal barrier function in rats.[97] VA can improve the morphology and structure of the intestinal tract after infection, regulate the relative expression of Mucin-2 and Occludin in the jejunal mucosa, and enhance the level of immunoglobulin in the serum, thus alleviating infection-induced intestinal dysfunction and IBD. This helps to protect the structural integrity of the intestinal tract and preserve its physical barrier.[98]

Vitamin D (VD) also plays an important role in regulating the intestinal gut flora. In an open study, researchers investigated the effects of high-dose oral vitamin D supplementation on the human intestinal microbiota in 16 healthy volunteers. Mucosal biopsies were obtained from the stomach, small bowel, and colon before and eight weeks after oral intake. The results showed that VD supplementation increased the levels of γ-protozoa, including Pseudomonas and Shigella, and reduced the relative abundance of harmful bacteria such as Aeromonas and Shigella, modulating the gastrointestinal microbiota through bacterial abundance.[98,99] In patients with CD, VD levels were lower in active patients than in those in remission.[100] Additionally, another mechanism by which vitamin D prevents IBD is by improving intestinal epithelial barrier function. Intestinal barrier permeability in patients with IBD has been linked to inflammation,[101] which can disrupt the immune system's interactions with the intestinal microbiota. A clinical survey of 198 patients with CD showed that vitamin D transduction is critical for maintaining epithelial barrier integrity through the expression of tight junction proteins (including Occludin, ZO-1, ZO-2, Vinculin, and Claudin), as well as modulating epithelial permeability.[102] Kong *et al*.[103] demonstrated that VDR-deficient mice have reduced trans-epithelial resistance, with impaired epithelial cell tight junctions, leading to susceptibility to DSS-induced colitis. In contrast, Liu *et al*.[104] demonstrated that overexpression of VDR in the colonic epithelium had a protective effect in several different mouse models of colitis, including DSS and T-cell overtransfer models, by preserving epithelial tight junctions and attenuating epithelial cell apoptosis. Furthermore, VDR on the mitochondria regulates mitochondrial respiratory activity by controlling the transcription of mitochondrial (COX2 and MT-ATP6) and nuclear (COX4 and ATP5B) proteins involved in respiratory activity and ATP synthesis.[105] Deficiency in either VDR or vitamin D leads to excessive mitochondrial respiratory activity, resulting in increased ROS production.[106] It is evident that adequate vitamin intake plays a crucial role in maintaining intestinal barrier homeostasis.

Conclusions

IBD is a chronic, relapsing inflammatory disorder of the intestinal tract that has become a global health problem. Although the etiology of IBD remains unclear, it involves multifactorial interactions between genetics, the environment, microbiota, and immune responses. The use of conventional clinical drugs, such as salicylates, glucocorticosteroids, and immunosuppressants, is no longer sufficient to meet the therapeutic needs of patients. However, the response of patients to existing drugs varies greatly, and some patients develop resistance, leading to a loss of efficacy. Therefore, the search for new therapeutic targets to improve the management of IBD is crucial. The intestinal mucosal barrier plays a critical role in maintaining intestinal homeostasis, including the development of the host immune system. Recent studies have demonstrated the roles of cellular autophagy, oxidative stress, and altered intestinal flora in the development of IBD. More research has led to unprecedented progress in our understanding of the pathogenesis of IBD. With advancements in gene technology, the molecular mechanisms of IBD will be more deeply revealed in the future, and the development of precision medicine will be promoted. In addition, the role of intestinal microbial populations in IBD should be further clarified. The specific mechanisms of microbial regulation therapies, such as probiotics and fecal microbiota transplantation, in repairing the intestinal barrier will be studied more thoroughly, and these will likely become important directions for future IBD research.

Acknowledgments

All authors declare that they have no commercial or associated interests in the submitted work.

Funding

This research was financially supported by the National Natural Science Foundation of China (grant number 81700472), the Natural Science Foundation of Shandong Province (grant number ZR2022MH1531), and the Clinical +X Project Fund of Binzhou Medical College (grant number BY2021LCX011).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Article design (ZZ, SZ, XL), article writing (ZZ), literature search (ZZ, RZ, RK), article review, and manuscript revision (YC). All author have approved the final version and publication of the manuscirpt.

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