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REVIEW

Restore Intestinal Barrier Integrity: An Approach for Inflammatory Bowel Disease Therapy

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Abstract: The intestinal barrier maintained by various types of columnar epithelial cells, plays a crucial role in regulating the interactions between the intestinal contents (such as the intestinal microbiota), the immune system, and other components. Dysfunction of the intestinal mucosa is a significant pathophysiological mechanism and clinical manifestation of inflammatory bowel disease (IBD). However, current therapies for IBD primarily focus on suppressing inflammation, and no disease-modifying treatments specifically target the epithelial barrier. Given the side effects associated with chronic immunotherapy, effective alternative therapies that promote mucosal healing are highly attractive. In this review, we examined the function of intestinal epithelial barrier function and the mechanisms of behind its disruption in IBD. We illustrated the complex process of intestinal mucosal healing and proposed therapeutic approaches to promote mucosal healing strategies in IBD. These included the application of stem cell transplantation and organ-like tissue engineering approaches to generate new intestinal tissue. Finally, we discussed potential strategies to restore the function of the intestinal barrier as a treatment for IBD.

Keywords: inflammatory bowel disease, intestinal barrier, pathophysiology, treatment

Introduction

Inflammatory bowel disease (IBD) represents a chronic, non-specific inflammation stemming from autoimmune disorders that predominantly impact the gastrointestinal (GI) tract. Typically, IBD manifests in two principal forms: Crohn's disease (CD) and ulcerative colitis (UC). While the exact etiology of IBD remains elusive, several factors have been confirmed to be associated with the disease processes, including environmental factors, genetic susceptibility, intestinal microbiota, and mental health problems.[1,2]

Significant distinctions exist between CD and UC, spanning systematic manifestations to molecular levels. For instance, UC primarily targets the colon, causing superficial mucosal inflammation that extends proximally in a continuous pattern. Conversely, CD can non-contiguously affect different segments of the digestive tract, characterized by transmural inflammation.[3] However, both CD and UC share dysfunctional or premature death of epithelial cells, a diminishing mucus layer, and dysregulated underlying intestinal immunity, resulting in compromised barrier protection.[4] The compromise of barrier integrity not only manifests clinically in IBD but also contributes to various alimentary diseases. This underscores a potential therapeutic avenue: the restoration of intestinal barrier integrity.[5]

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The components of the intestinal barrier typically include three sections: the mucus layer, the mucosa, and the underlying mucosal immune system.[6] The intestinal epithelium comprises a single layer of epithelial cells interconnected with tight junctions (TJs), playing a crucial role in regulating interactions among intestinal contents (eg, microbiota), the immune system, and other components.[3,7] The diverse intestinal epithelial cells, each with unique functions, maintain intestinal health, and any reduction in their quantity or diversity weakens the epithelium's protective and digestive capacity.

The mucus barrier functions as a crucial protective layer in the GI tract, serving as the initial defense against bacterial invasion.[8,9] Goblet cells are the principal producers of mucus.[10] Beneath the epithelial layer, the intestinal immune system provides defensive capabilities. A multitude of immune cells resides within the GI tract, either in organized anatomical structures such as Peyer's patches and mesenteric lymph nodes or dispersed throughout the intestinal epithelium and lamina propria.[11] Unlike the immune systems of other organs, the intestinal immune system autonomously down-regulates immune reactions to sustain an anti-inflammatory environment in a healthy state.[3] In the unique environment of the intestine, filled with exogenous antigens (eg food antigens), the intestinal immune system must defend against pathogen invasion while preventing excessive immune damage to its tissues.[12] Consequently, intestinal immunity maintains a dynamic balance.[3] Typically, effector immune cells produce inflammatory factors to prevent infection, while regulatory cells inhibit inflammation.[13] In a healthy state, intestinal macrophages produce large amounts of the anti-inflammatory interleukin (IL)-10 when exposed to bacteria, and dendritic cells (DCs) produce retinoic acid and transforming growth factor β (TGF-β) to promote the generation of regulatory T cells (Tregs).[3]

To uphold the integrity of the barrier, heightened attention must be directed towards the molecular mechanisms governing barrier function in IBD, particularly focusing on epithelial cell junctions. Cell junctions establish connections between adjacent epithelial cells and the extracellular matrix (ECM), unifying the epithelium. They also regulate the selective permeability of the epithelium, enabling it to control paracellular transportation.[6] Among various types of junctions, TJs play a pivotal role in determining cell junction function.[6,14] Consequently, the absence of TJs significantly compromises defense, a common characteristic observed in IBD (Figure 4).

Furthermore, the process of intestinal mucosal healing is intricate, involving the migration and proliferation of intestinal epithelial cells (IECs) and the regulation of intestinal microbial peptides, such as mucins, growth factors, and defensins, along with the involvement of various molecules.[15,16] Simultaneously, the complex mechanisms underlying mucosal repair offer diverse therapeutic targets for restoring intestinal integrity. However, current IBD therapies predominantly focus on inflammation suppression, with no disease-modifying therapies available targeting the restoration of epithelial barrier integrity.[17] Consequently, there is promising potential for further investigation into the intestinal barrier to propose more effective alternative therapies for IBD.

This review aims to elucidate the components of the intestinal barrier and their respective roles, along with delineating the changes occurring in the barrier within the context of IBD. Subsequently, we delve into the self-repair process of the intestinal barrier and the involved mechanisms. In the course of this exploration, we pinpoint therapeutic targets unearthed in the repair program, thereby prompting the contemplation of potential strategies aimed at reinstating both the function and integrity of the intestinal barrier in the treatment of IBD.

Components and Mechanisms of the Intestinal Barrier

Epithelium

The intestinal epithelium, constituting the innermost layer of the intestinal barrier, forms the lining of the GI tract. Comprising six specialized cell lineages, enterocytes (absorptive cells), microfold cells (M cells), goblet cells, Paneth cells, hormone-producing enteroendocrine cells (EECs), and stem cells (Figure 1).[17] The epithelium plays a crucial role in maintaining barrier function. Enterocytes and M cells primarily facilitate absorption, while goblet cells, Paneth cells, and EECs are in charged of secretory mission.[18] Enterocytes, the most abundant cells in the intestinal epithelium, significantly expand the surface area to enhance nutrient absorption.[19] Another differentiated cell type, tuft cells, resemble enterocytes and are primarily responsible for sensing and responding to various signals involved in immune responses, particularly type 2 mucosal immunity.[20,21]

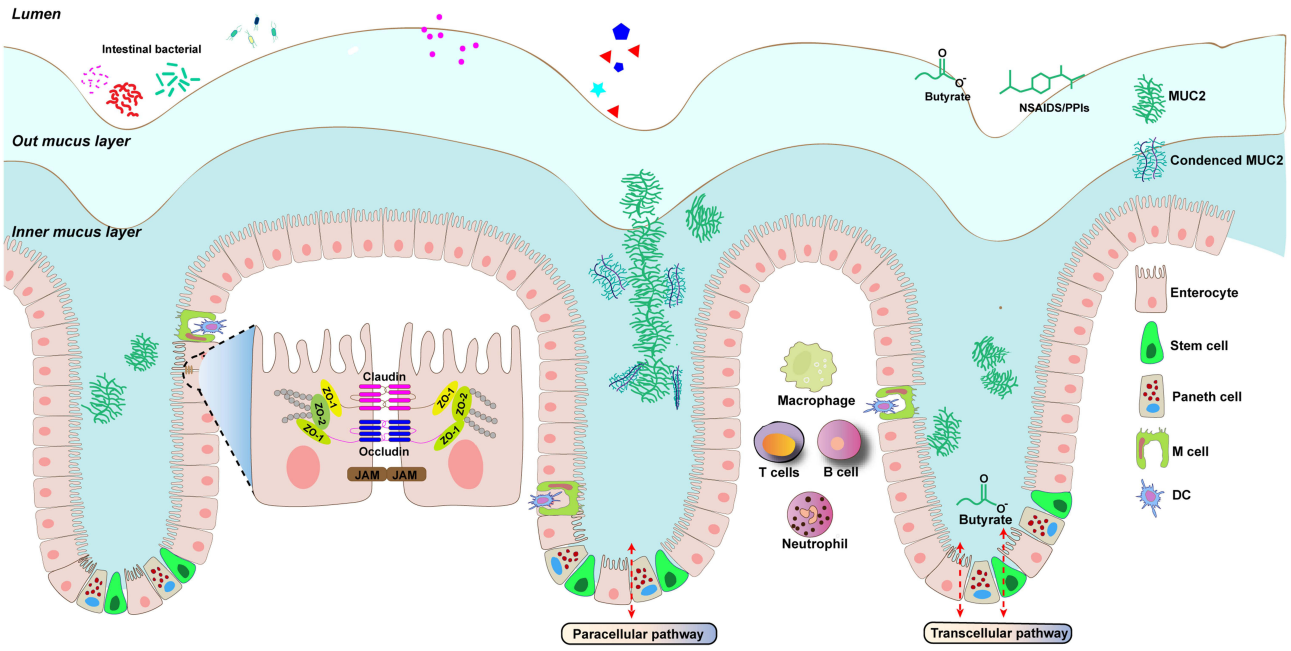

Figure 1 Illustration of the structure and functions of intestinal barrier. The intestinal barrier consists of a chemical barrier and a physical barrier. The epithelial cells form a physical barrier consisting of tight junction-associated proteins, including occludin, claudin; JAM: junctional adhesion molecule. These tight junction protein components close off the paracellular pathways and function as gates and fences. The mucus layer is a chemical barrier consisting of a dense inner layer and a lax outer layer that is essential for prevent invading microorganisms and the host. The skeleton that makes up the mucus layer is primarily MUC2. Immune cells are also involved in the immune response and host tolerance to external substances. Damage to the intestinal barrier leads to infiltration of intestinal microorganisms from the lumen into the lamina propria, inducing immune stress in host immune cells.

M cells play a pivotal role in sampling gut contents and facilitating the transportation of luminal antigens to immune cells located in Peyer's patches.[22] Goblet cells, crucial in producing a protective mucus layer and secreting IgA to resist pathogens, also serve as antigen couriers conveying signals from the intestinal lumen to the underlying immune system.[10,23] This initiates time-specific and location-specific processes to induce adaptive immune responses.[10,24] Paneth cells contribute to the production of antimicrobial peptides (AMPs), including alpha-defensins, lysozyme, and secretory phospholipase A.[3] Notably, the higher concentration of negatively charged phospholipids in bacterial cell membranes enables defensins to selectively and preferentially bind to them[25]. EECs synthesize and secrete different hormones to regulate digestive movement.[26] Intestinal stem cells (ISCs), residing at the base of the crypts, give rise to all absorptive and secretory cells (Table 1).[27,28] In the context of IBD, both the functionality and quantity of epithelial cells

Table 1 Cell Types and Their Functions in the Composition of Intestinal Epithelium

Cell Lineage	Type	Main Function
Enterocytes	Absorptive cells	Promote absorption, expand surface area for efficient nutrient absorption
Microfold cells (M cells)	Absorptive cells	Play a vital role in sampling gut contents, facilitate transportation of luminal antigens
Tuft cells	Absorptive cells	Sense and respond to signals involved in immune responses, especially type 2 mucosal immunity
Goblet cells	Secretory cells	Produce mucus layer, secrete IgA for pathogen resistance, convey signals for immune responses
Paneth cells	Secretory cells	Produce antimicrobial peptides (AMPs) like alpha-defensins, lysozyme, and secretory phospholipase A
Enteroendocrine cells (EECs)	Secretory cells	Synthesize and secrete hormones to regulate digestive movement
Stem cells	Stem cells	Reside at the base of crypts, give rise to all absorptive and secretory cells

Abbreviations: M cells, Microfold cells; EECs, Enteroendocrine cells; AMPs, antimicrobial peptides;

are compromised, resulting in a weakened protective function of the epithelium. This impairment highlights a significant aspect of IBD pathology.

Cell Junction

The epithelial barrier's functionality hinges on both a contiguous layer of cells and the existence of paracellular space between these cells. Cell junctions play a crucial role by binding epithelial cells into a cohesive unit and regulating selective paracellular transportation.[6] In an inflammatory state, the contiguous layer breaks down, accompanied by an upregulation in paracellular conductance, indicating the involvement of TJ dysfunction. Within the intestinal epithelium, intercellular junctions include TJs, adherens junctions (AJs), and desmosomes, collectively referred to as the apical junctional complex (Figure 1).[29]

TJs form an apical belt-like structure around IECs and are integral in maintaining the integrity of the epithelium and restricting material exchange.[29] Destruction of TJs has been identified in IBD, leading to barrier leakage that permits the passage of bacteria.[25] Therefore, restoring the quantity and function of TJs has become a promising therapeutic strategy for IBD.

TJs consist of a complex network of specialized proteins, broadly categorized into transmembrane proteins, cytosolic plaque (scaffolding) proteins, and regulatory proteins.[6,30] Transmembrane proteins include claudin, occludin, and junctional adhesion molecule (JAM), with claudin being particularly crucial.[31,32] Claudins form pores by connecting with corresponding claudins on adjacent cells, regulating the selectivity of TJs.[5] For instance, studies have revealed that claudin-2 constructs pores with ion selectivity, and its absence increases paracellular ion conductance without a concomitant increase in the flux of larger molecules.[33–35] Gates of these pores exist in a dynamic state of opening and closing, similar to transmembrane ion channels, presenting a potential target for regulating barrier function.[34] Occludins, tetraspanning proteins located at the cell-cell surface membrane, are phosphorylated by myosin light chain kinase (MLCK)-1, triggering their endocytosis and increasing TJ permeability.[30,36] JAMs facilitate TJ assembly and leukocyte transmigration, and their absence increases susceptibility to inflammation.[6,37] Cytosolic plaque proteins like ZO proteins directly interact with transmembrane TJ proteins and the actin cytoskeleton, regulating junction assembly.[38]

AJs comprise cadherin adhesion receptors and associated cytoplasmic proteins, such as actin filaments.[39] E-cadherins form adhesive dimers at cell-cell boundaries, and their interaction with p120 catenin and β-catenin on the cytoplasmic side, followed by α-catenin binding to β-catenin, establishes the cadherin–catenin core complex.[39–41] AJs connect adjacent cells and the actin cytoskeleton, establishing a robust cell-cell connection. In vitro studies suggest that AJs facilitate TJ assembly through E-cadherin and α-catenin.[42,43] Furthermore, AJs are dynamic structures regulated by the cytoskeleton, enabling tissues remodeling in response to damage.[39]

Three pericellular pathways exist in TJs: pore, leak, and unrestricted pathways.[44] Pore pathways, regulated by claudin proteins, are high-capacity, charge- and size-selective routes.[45–47] Leak pathways are size-selective and regulated by occludin, tricellulin, ZO-1, and perijunctional actomyosin.[44] In healthy gut conditions, these pathways reflect TJ permeability.[44] However, in severe UC, particularly at sites of extensive epithelial damage, the unrestricted pathway allows the passage of massive ions, macromolecules, and even whole bacteria through the intestinal barrier.[5] Complex mechanisms regulate these pathways, offering potential therapeutic targets to reduce barrier permeability. For instance, casein-kinase-2 can induce the phosphorylation of occludins, and inhibiting this process accelerates the assembly of the TJ complex while restricting passage through claudin-2 pores.[48] As a result, cell junctions hold the potential to identify pericellular permeability-regulating mechanisms, representing future therapeutic targets for IBD.

Mucus Layer

Mucus, a crucial component of the intestinal barrier, is composed of materials originating from the epithelium, predominantly produced by goblet cells. Key constituents include mucin-2 (MUC2), Fcγ binding protein (FCGBP), calcium-activated chloride channel regulator1 (CLCA1), and others (Figure 1).[10,49,50] The mucus core is primarily comprised of MUC2, a densely glycosylated protein that serves as a skeleton, forming a multimeric and crosslinked network.[10,51,52] Upon secretion into the intestinal lumen, the alkaline environment and the removal of calcium ions cause the unfolding of MUC2, leading to its expansion and the formation of a net of stratified mucus gel.[53,54] Na^+/H^+

exchanger 3 (NHE3), a reverse transport protein expressed on the apical surface of IECs, constructs an acidic environment beneath the outer mucus layer. This acidic environment may contribute to the formation of the compact inner mucus layer by maintaining the tight structure of MUC2.[55,56]

Electron microscopy has revealed the predominantly reticular three-dimensional structure of mucus, featuring minute pores.[57] This unique structure, along with its electrostatic properties, selectively blocks the movement of substances.[10,58] The outer mucus layer is loose, allowing bacteria to enter and colonize, and is easily cleared out. In contrast, the inner layer is tightly structured, preventing bacterial penetration.[23,52,53] Nevertheless, the permeability of the inner layer is not uniform across all regions, influenced by two types of goblet cells that produce distinct mucus. Goblet cells residing in the intestinal crypts secrete a dense mucus effective against bacteria, whereas inter-crypt goblet cells on the colonic epithelial layer produce a relatively penetrable mucus.[58] The distinct properties of different mucus types enable the inner layer to prevent bacterial invasion while facilitating substance exchange.[58]

Mucus is secreted in response to damage factors, such as mechanical stress, elevated levels of microbial ligands, or ischemia.[49,59–62] The mucus layer can execute rapid self-recovery after a certain level of injury. However, when the extent of mucosal injury surpasses a threshold or when damage factors persist, the self-repair capacity becomes insufficient to compensate. This situation is comparable to mucus dysfunction observed in IBD.[55,63]

The mucus layer serves as a multifunctional protective barrier in the intestine, forming a physical shield that covers the intestinal wall and encapsulates fecal matter. This barrier prevents direct contact between harmful substances and the epithelium.[10,64,65] Additionally, mucus provides lubrication, facilitating the smooth passage of gut content and reducing the risk of mechanical damage.[9,10,66] With its sticky texture and multi-layered net structure, mucus can effectively trap pathogens and undergo constant renewal through coordinated muscular contractions, thereby expelling trapped pathogens from the gut.[67–69]

Vitally, mucus plays a crucial role in maintaining gut microbiota homeostasis.[6,8] The mucus layer includes specific carbohydrates that serve as an energy source for certain commensal bacteria, fostering the growth of beneficial symbiotic bacteria and hindering the colonization of invasive pathogens.[70,71] Consequently, strategies focused on restoring mucus and its function have the potential to alleviate IBD. This emphasizes the significance of regarding mucus as a therapeutic target for interventions in IBD.

The Self-Repair Mechanism of a Healthy Intestinal Epithelium

Apart from the previously mentioned protective barrier, the self-renewal capability for restoring intestinal integrity plays a crucial role in defending against damaging factors (Figure 1). The healthy epithelium undergoes updates every four to 7 days.[72,73] When the epithelium is damaged, adjacent epithelial cells gradually lose their columnar morphology, migrate toward the damaged area, and subsequently cover the wound in a process known as "epithelial restitution".[27] In the regeneration process, $LGR5^+$ stem cells serve as the "origin" of the repair process. $LGR5^+$ stem cells, a subtype of ISCs, express the LGR5 protein and possess high regenerative and differentiation potential.[28,74–76] Primarily located at the crypt base of the small intestine and colon, these cells undergo programmatic activation, migrating upwards along the crypt-villus axis. During this process, ISCs undergo proliferation and differentiation and ultimately fill the gaps in epithelial damage.[77] The intricate molecular mechanisms regulating this process highlight its complexity.

The repair process relies on signaling originating from the microenvironment, which is constructed by various cells, ECM, and more.[77] Mesenchymal cells residing below the epithelium in the lamina propria secrete various factors into the microenvironment, playing essential roles in the repair process.[3,78] For instance, $FOXL1^+$ telocytes and GLI1-expressing mesenchymal cells, acting as important sources of Wnts, activate the Wnt/β-Catenin signaling pathway, promoting the proliferation of ISCs and transit amplifying cells.[79,80] Fibroblasts produce IL-33, which directly acts on $LGR5^+$ cells and promotes their differentiation towards the secretory lineage by suppressing Notch signaling.[81] $CD34^+$ $Gp38^+$ fibroblasts upregulate the expression of Grem1, Rspo1, Wnt2b, and several chemokines, cytokines, and epithelial growth factors, participating in immune response and wound repair.[82–84] Enteric glial cells (EGCs) enhance wound repair by promoting the spreading of IECs through pro-epidermal growth factor (EGF) secretion.[85] Paneth cells, located at the base of the niche adjacent to ISCs, provide essential signals such as Delta-like 1/4, EGF, and Wnt to support ISC homeostasis.[86,87]

Additionally, the ECM can activate mechanical sensors, such as Yes-associated protein (YAP) and Tafazzin (TAZ), suppressing adult stem cell markers and reprogramming them into a primitive state.[88]

Moreover, studies have demonstrated that the underlying immune system regulates barrier restoration, with immune cells secreting cytokines with distinct protective effects.[77] IL-6 can activate STAT3 and YAP to promote epithelial regeneration.[89] Group 3 innate lymphoid cells (ILCs) secrete IL-22 in response to damage, inducing the phosphorylation of STAT3 in CBCs, subsequently enhancing organoid growth without activating the Wnt or Notch pathway.[90,91] IL-10, rapidly secreted by macrophages upon intestinal injury, promotes epithelial proliferation through epithelial cAMP response element-binding protein (CREB) signaling and subsequent WNT1-inducible signaling protein 1 (WISP-1) secretion.[92] Additionally, the host's nutritional state also affects the repair process, as calorie restriction and a high-fat diet can induce the expansion of the ISC pool.[93] In summary, given the epithelial damage in IBD, studies focused on the mechanisms involved in the repair process can identify therapeutic targets with the potential to facilitate epithelium restoration.

Intestinal Barrier Dysfunction in IBD Disease

The integrity of the intestinal barrier is significantly compromised in the context of IBD. This impairment can be primarily attributed to abnormalities in five key elements: epithelial cells, cell junctions, the mucus layer, the intestinal immune system, and commensal microbiota. Due to the complex interactions among these defenders, their dysfunctions can mutually exacerbate each other, potentially establishing a vicious cycle. Consequently, interrupting this cycle at an intermediate stage becomes crucial for controlling the progression of the disease.

Interplay of IEC Death and Immune Dysregulation in Barrier Disruption

During the active phase of IBD, an upregulation of programmed cell death within the intestine significantly compromises the integrity of the intestinal barrier. The premature death of stem cells has particularly serious consequences, inherently weakening the regenerative capacity of the epithelium.[84,94] Common forms of programmed cell death include anoikis, apoptosis, necroptosis, and pyroptosis.[84] In a healthy state, IECs undergo regular self-renewal, with cells shedding through apoptosis without triggering an inflammatory response.[95]

In individuals with IBD, there is an excessive apoptosis of IECs attributed to the synergistic effects of genetic susceptibility and environmental damaging factors.[96] Macrophages, unfortunately, are unable to promptly clear these cells, resulting in secondary necrosis and pyroptosis, thereby triggering inflammation. The sustained and excessive release of inflammatory factors can fuel an overactive immune response, thereby contributing to the progression of autoimmune diseases such as IBD.[97] In a healthy intestine, apoptotic IECs are engulfed by macrophages. Subsequently, macrophages undergo M2 polarization and metabolic switching, generating eicosanoids such as prostaglandins (PGs) and resolvins. These substances promote tissue repair and angiogenesis and suppress the immune system.[84] Simultaneously, DCs sense cellular debris, transition to a tolerogenic state, and migrate to the mesenteric lymph nodes. There, regulatory T cells (Tregs) are activated and proliferate, suppressing effector T cell responses.[84]

In contrast, necroptotic or pyroptotic cell death, followed by the release of damage-associated molecular patterns (DAMPs), induces M1 polarization of macrophages and a pro-inflammatory transition of DCs.[98] M1 macrophages secrete pro-inflammatory cytokines (IL-1β, IL-36, etc.), activating effector T cells in the lymphoid node and fibroblasts.[99] DCs migrate to the mesenteric lymphoid node and present antigens, activating naive T cells (Tn) while inhibiting the activation of Tregs.[84]

The therapeutic potential of macrophage state switching in IBD has gained significant attentions recently. A recent study has found that turmeric-derived nanovesicles (TNVs) alleviate colitis-related symptoms by restoring the intestinal epithelial barrier. TNVs can suppress the expression of CD16/32 and increase the expression of CD206 in the colonic lamina propria, promoting the conversion of M1 to M2 macrophages.[100] Additionally, CS-IGF-1C hydrogel has been found to alleviates inflammatory responses through PGE2-mediated polarization of M2 macrophages.[101] Moreover, it has found that the HA/CS/Dex nanoparticles (HCD NPs) could be internalized by macrophages, thereby regulating the polarization from M1 to M2 macrophages and exerting anti-inflammatory effects.[102] This mechanism provides a safe, feasible, and effective approach for treating ulcerative colitis.[100]

In the context of IBD, the progression of inflammation encompasses several crucial steps. The initial stage involves the activation of the inflammatory cell death pathway by environmental signals, culminating in pyroptosis or necrosis of IECs and the subsequent release of DAMPs. Pattern recognition receptors (PRRs) on both epithelial and immune cells identify specific stimuli, such as signals of tissue damage or infection.[103–106] Once recognized, these receptors form inflammasomes with adaptor proteins and pro-caspases, activating caspases.[107] Activated caspases cleave and translocate gasdermin D (GSDMD) to the cell membrane, creating pores that lead to the leakage of DAMPs into neighboring tissues.[104,108] Simultaneously, inflammasomes mature pro-inflammatory cytokines (such as pro-IL-1β and pro-IL-18) and release them into surrounding tissues through cell membrane pores.[95,99,109]

As cell death advances, GSDMD molecules undergo cleavage, subsequently forming pores. This process leads to membrane rupture and the release of cellular contents into the surrounding tissue.[110] DAMPs represent a class of molecular motifs typically released as endogenous molecules when cells are damaged or dead.[111] Recognized by the immune system, these molecules can induce inflammatory responses.[111] Under normal circumstances, these molecules are selectively expressed and sequestered within the nucleus, mitochondria, and cytoplasm, avoiding direct interaction with the immune system.[105,112] Examples include double-stranded DNA (usually confined to the cell nucleus), ATP (commonly found in the cytoplasm), and various molecules existing at high concentrations exclusively within the mitochondria.[105] In addition to releasing molecules typically sequestered inside cells, DAMPs may also encompass modified components of the ECM, such as hyaluronic acid (HA).[105]

The second step involves the activation of immune cells and the release of pro-inflammatory factors. DAMPs are recognized by PRRs on sentinel cells, including macrophages, DCs, and ILCs. This recognition prompts these sentinel cells to produce pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-1, histamine, nitric oxide (NO), reactive oxygen species (ROS), PGs, and leukotrienes.[105,106,113] Ultimately, the uncontrolled release of pro-inflammatory cytokines triggers adaptive immune dysregulation, resulting in dysfunction of the immune system and loss of tolerance to normal tissues and organs.[96] In this scenario, autoantibodies and self-reactive T cells may erroneously attack the intestinal tissues, contributing to the progression of IBD inflammation.[12,97,114–116]

As research progresses, numerous therapeutic targets have been identified in this process. In patients with IBD, particularly those with UC, an increased expression of GSDMD has been observed in the intestinal mucosa.[99] This heightened expression can stimulate IECs to release IL-1β, thereby enhancing the inflammatory response. Experimental evidence also indicates that mice with GSDMD defects exhibit reduced inflammation in response to dextran sulfate sodium (DSS) induction.[99]

Studies have found that SETDB, a histone methyltransferase, safeguards genome stability. In patients with IBD, its decreased expression leads to genome instability of ISCs and induces Z-DNA binding protein 1 (ZBP1)-mediated necroptosis.[117,118] Therefore, interfering with the sensing of endogenous retrovirus (ERV) RNA by ZBP1 may hold potential therapeutic benefits for patients with IBD.[117] Additionally, upregulated TNF-α has been found to promote necroptosis of ISCs, especially active $LGR5^+$ ISCs sensitive to acute injury. Prostaglandin E2 (PGE2) has a potential targeted therapeutic effect, as it can facilitate the expansion of $LGR5^+$ ISCs via EP2-mediated signaling.[119] Furthermore, it has been discovered that XBP1 deletion triggers endoplasmic reticulum (ER) stress, heightening the sensitivity of IECs to cell death and subsequently contributing to the spontaneous apoptosis of differentiated Paneth and goblet cells.[120]

Mitochondrial metabolism dysbiosis has also been identified as relevant to IBD. Prohibitin 1 (PHB1), a major component of the inner mitochondrial membrane, is absent in ISCs, leading to spontaneous ileal inflammation, which can be reversed with a mitochondrial-targeted antioxidant.[121] Studies have also discovered that deletion of heat shock protein 60 (Hsp60) in ISCs induces mitochondrial dysfunction, resulting in reduced $LGR5^+$ expression and then inhibiting the differentiation of $LGR5^+$ cells into Paneth cells.[122] Dichloroacetate (DCA) regulates mitochondrial disorders by diminishing glycolysis and improving mitochondrial respiration, presenting the potential to prevent IBD recurrence.[122] Thus, therapies aimed at enhancing epithelial renewal ability or inhibiting cell death provide therapeutic modalities for IBD.

Increased Barrier Permeability

In the context of IBD, an increase in barrier permeability and abnormalities in cell junctions have been observed.[25,123] These manifestations in IBD are associated with the upregulation of inflammatory factors, such as TNF-α, IFN-γ, and interleukin.[124,125] TNF-α, for instance, facilitates the phosphorylation of the myosin light chain (MLC), leading to a decrease in occludins, and an increase in conductance through the leak pathway.[36,126–130] Simultaneously, the Th2 cytokine IL-13 induces the expression of claudin-2, resulting in increased pore pathway flux.[6,94,128] IFN and TNF synergistically affect TJs by upregulating each other's receptors.[131,132] High doses of TNF and IFN can reduce zonula occludens (ZO), further compromising the protective function of TJs.[133,134] In CD, there is a predominant increase in IFN and TNF levels, while in UC, the primary elevation is observed in IL-13 and TNF, leading to a significant increase in claudin-2 (Figure 2).[94,128,135]

Active CD patients exhibit distinctly impaired intestinal barrier function. Despite the presence of localized epithelial lesions, freeze-fracture electron microscopy reveals that discontinuous TJ strands contribute to the dysfunction of the intestinal barrier.[94] In the active state of IBD, there is a significant decline in the expression of claudin 5 and claudin 8, which inhibits cation permeability, whereas there is a notable upregulation of claudin 2, which forms pores.[94]

During the remission phase of CD, TJ proteins are almost restored, and cell necrosis is basically under control, leading to normalized barrier function.[94] Unexpectedly, some research has indicated that certain patients still exhibit distinct increased intestinal permeability.[136,137] Further studies have subsequently demonstrated that the upregulated permeability is caused by increased transcellular transport, primarily mediated by immune-epithelial interactions, rather than ascending pericellular conductance.[138] For example, CD23, a low-affinity receptor for IgE, is overexpressed at the apical surface of intestinal cells in CD, leading to increased transcellular transport of IgE-allergen immune complexes from the intestinal lumen to the lamina propria, subsequently triggering mast cell degranulation and allergic inflammatory responses in the subepithelial immune system.[139] IIn general, in the inflamed region, the transportations through both pericellular and transcellular pathways increase, resulting in excessive stimulation to the local intestinal immune system, which, in turn, promotes inflammation.[25,139] This process ultimately forms a vicious spiral, inducing the deterioration of barrier function.

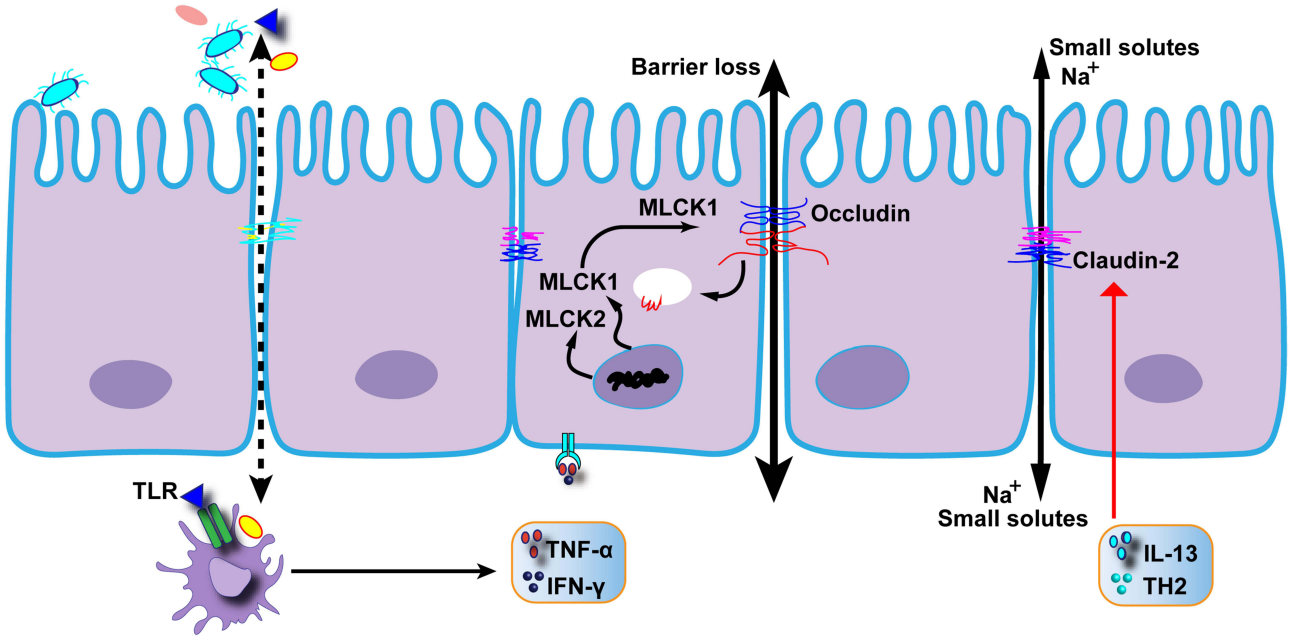

Figure 2 The molecule diverts a key signaling molecule away from the intercellular junctions that regulate the intestinal barrier, preventing the immune system from disrupting the barrier.

Mucus Layer Alterations

The protective capability of the mucus layer is weakened in patients with IBD, contributing to increased bacterial penetrability.[49,140,141] Tissue biopsies of UC patients reveal that the mucus layer becomes thinner and even absent in certain areas, and this change is independent of local inflammation.[49,142] However, this phenomenon is not absolute. In IL-10 knockout mice, an unexpected increase in mucus layer thickness has been observed, possibly as a compensatory response to the weakened function of the mucus barrier.[141] However, the quality of the mucus secreted in compensation is often inferior.[52] The mechanisms underlying the thinner and poor-quality mucus layer are complex.

The primary underlying factor is the malfunction of mucus producers in IBD. Examination of tissue biopsies from patients experiencing active IBD reveals a distinct reduction in mature goblet cells, likely stemming from a combination of factors such as excessive mucus release, diminished mucus storage, altered goblet cell differentiation, and increased apoptosis.[49,143] Substantial support for this hypothesis is provided by the noticeable decline in sentinel cells.[49,53] In the case of patients with remission in UC, biopsies indicate a decrease in mitochondrial β-oxidation, potentially disrupting goblet cell differentiation.[144] Although the overall number of goblet cells remains relatively constant during the remission period, specific subtypes experience a reduction.[141] For instance, inter-crypt goblet cells are prematurely shed during the remission phase, resulting in the absence of inter-crypt mucus. This suggests a potential link between defective inter-crypt mucus and the initiation of IBD.[10,58]

Moreover, the antibacterial protein WFDC2, secreted by goblet cells, is dysregulated in IBD. Given that WFDC2 inhibits the activity of serine and cysteine proteases, preventing the premature conversion of the inner mucus layer to the outer layer, its deficiency can lead to abnormal mucus layer formation, facilitating bacterial invasion.[145] Additionally, electron microscopy has revealed the accumulation of incompletely synthesized or misfolded MUC2 mucin in the ER, indicating heightened ER stress in goblet cells.[146] Recent studies suggest that elevated ER stress has the potential to inhibit the production of MUC2, thereby triggering the progression of IBD in the early stages.[53,147–149]

Mucus barrier dysfunction stems from structural irregularities and disrupted formation of the mucus layer. The aberrant mucus demonstrates reduced glycosylation, shortened oligosaccharide side chains, diminished sulfation, and a decrease in core mucus proteins.[49,150,151] Additionally, early investigations have pinpointed the downregulation of the chloride anion exchanger SLC26A3 and the malfunction of sodium-hydrogen exchangers in IBD, both pivotal in mucus layer formation.[56,152–154]

Moreover, emerging research highlights the impact of dietary habits and the dysbiosis of the intestinal microbiota in the IBD process. Dietary fibers serve as the primary energy source for the microbiota in the lower GI tract.[155] Certain microbial species, such as *Bacteroides thetaiotaomicron, Bifidobacterium bifidum, Ruminococcus gnavus, Ruminococcus torques*, and *Akkermansia muciniphila*, can utilize glycans for mucus barrier formation.[53,156,157] Chronic and intermittent dietary fiber deficiency amplifies the survival competitiveness of bacteria dependent on mucins as a food source. As these bacteria proliferate, mucins are continually depleted, leading to a gradual thinning of the mucus layer.[53] Consequently, the diminished mucus layer becomes more susceptible, facilitating bacterial penetration.

Dysbiosis in the GI Microbiomes

A noticeable alteration in the density and composition of intestinal bacteria has been identified, contributing to microbiota dysbiosis in individuals with IBD.[53] In healthy individuals, the predominant bacterial phyla include *Firmicutes, Bacteroidetes, Proteobacteria*, and *Actinobacteria*.[158] The microbiota in the lower GI tract primarily utilize dietary fiber as their energy source.[155] Fibrolytic bacteria break down polysaccharides into smaller carbohydrates, subsequently fermenting them into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate.[159] SCFAs exhibit immunomodulatory properties and stimulate the proliferation of Tregs in the intestine.[160–164]

Particularly noteworthy is butyrate's ability to induce the expression of the actin-binding protein synaptopodin (SYNPO), promoting the repair of intestinal epithelium. Butyrate also serves as the primary energy source for colonocyte.[39,163–165] Research has demonstrated a reduction in SCFA-producing bacteria in the context of IBD, leading to a gradual loss of the protective effects provided by SCFAs.[25,162,166]

Although these dysfunctions have been identified in the IBD process, the causality linking the onset of IBD to these dysfunctions, along with the intricate interplay among different dysfunctions, still requires clarification. Further research is essential to illuminate the pathogenesis of IBD, pinpoint suitable therapeutic targets, and subsequently devise effective treatment approaches aimed at restoring barrier integrity.

Current Therapeutic Strategies That Improve Barrier Dysfunction

Current therapies for IBD can be broadly categorized into two groups: untargeted treatments, including amino salicylates, glucocorticoids, and immunosuppression, and targeted biologic therapies, such as anti-TNF, anti-IL-12/IL-23, anti-α4β7 integrin, IL-10, and IL-22.[15,167–170] Although biological therapies demonstrate efficacy for a substantial number of patients, around 30% do not respond to initial treatment, and up to 50% experience a loss of response over time.[171] Notably, certain medications, especially steroids and immunomodulators, exert broad immunosuppressive effects, elevating the risk of infectious and neoplastic events.[15,171] Consequently, there is a growing interest in therapies focused on restoring intestinal barrier integrity (Figure 3).

Stem Cells Transplantation

Promoting the proliferation and differentiation of stem cells emerges as a promising therapeutic strategy, with three noteworthy methods outlined below. Firstly, the engraftment of ISCs has been explored.[172] Early research indicates that the therapeutic efficacy of enema-based transplantation of ISCs is notably limited and becomes apparent primarily in the presence of persistent damaging factors.[173] However, transplantation of mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) has demonstrated effectiveness.[174,175] The second approach involves the culture and

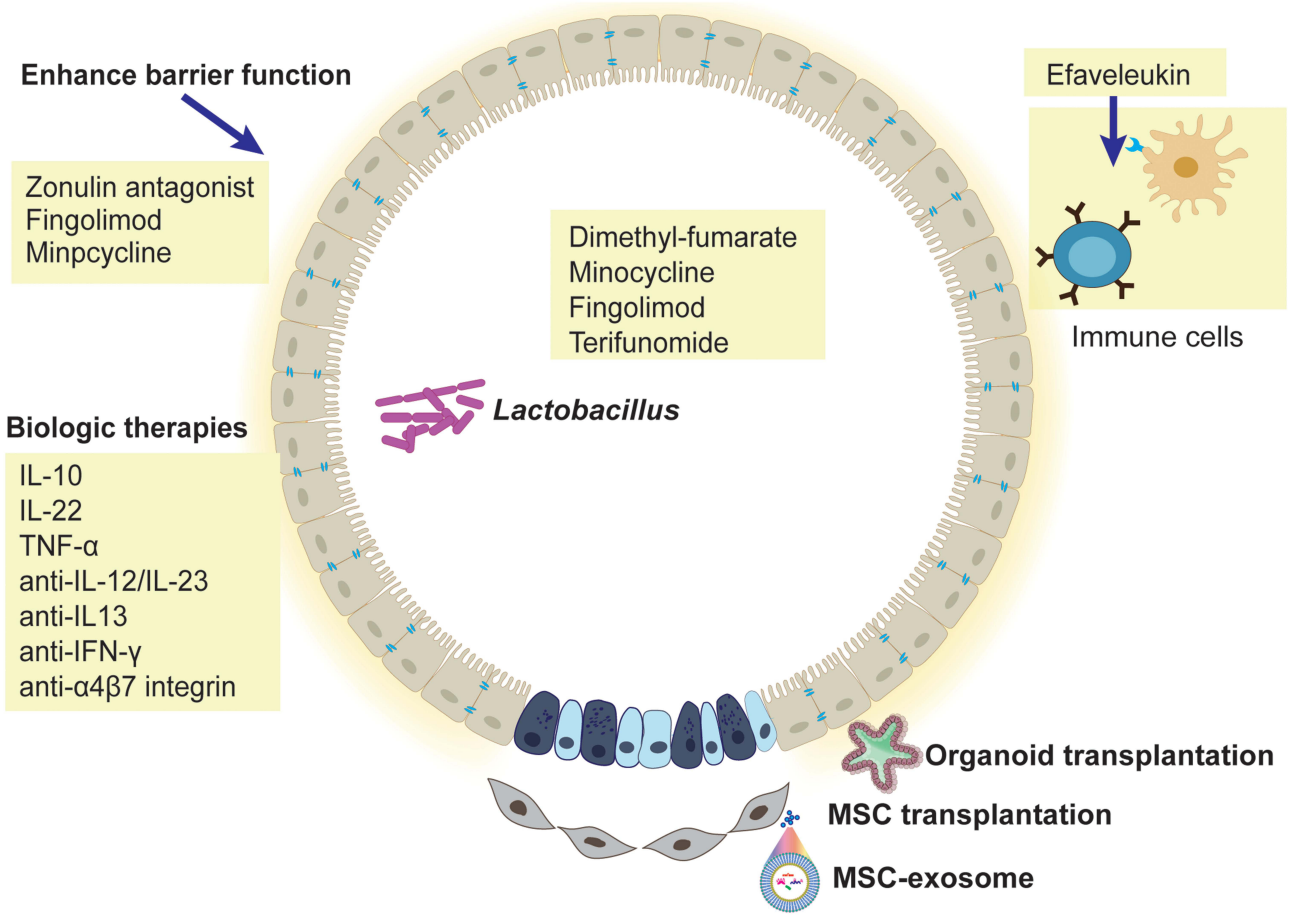

Figure 3 Possible therapeutic strategies to improve the intestinal barrier function.

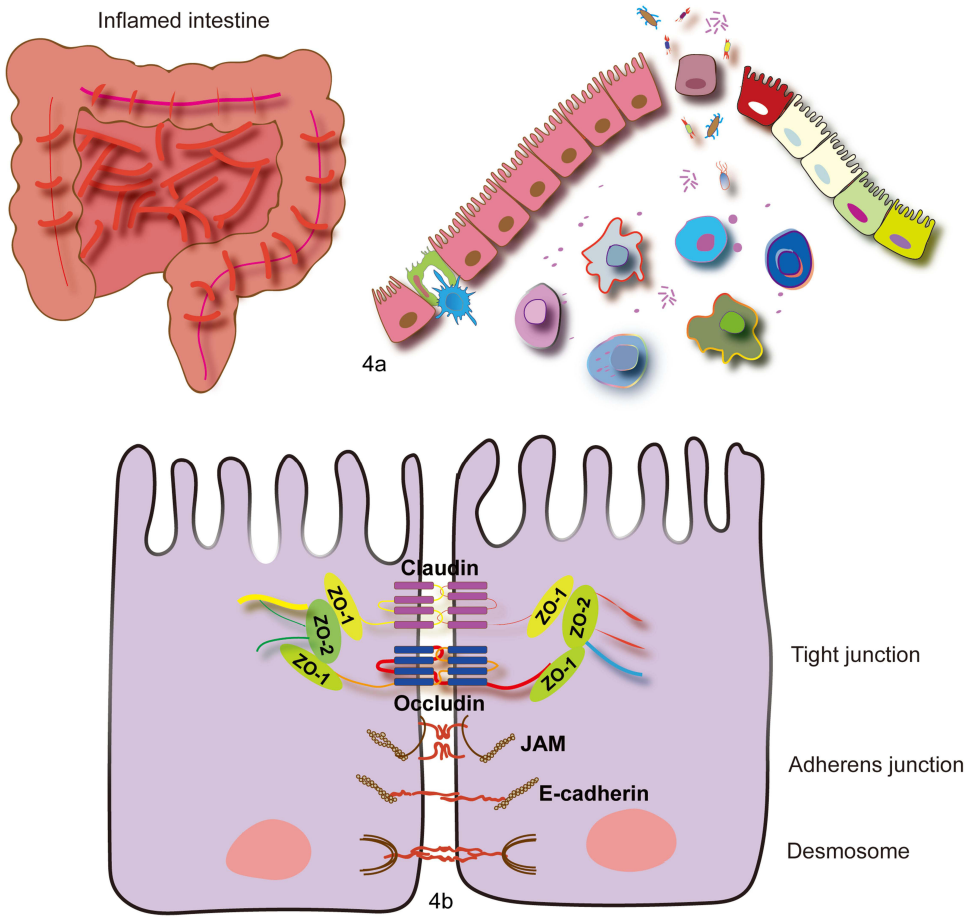

Figure 4 (**a**) Structural and functional modulation of the intestinal epithelial barrier under IBD will provide new ideas for the development of therapies for such chronic diseases. (**b**) The cell junctions of intestinal epithelium are disrupted in inflammatory bowel disease, providing potential targets for treatment.

transplantation of organoids.[176] Organoids, possessing a structure and cellular composition akin to the intestinal epithelium in the body, prove beneficial.[87] This property facilitates the engraftment of intestinal organoids at damaged mucosal sites, thereby accelerating the healing of inflamed mucosa.[173,177] Additionally, through the in vitro expansion and transplantation of autologous ISCs, the risk of rejection can be effectively minimized.[168,174] The third strategy aims to enhance epithelial expansion. EGF and R-spondin-1 play crucial roles in epithelial growth.[6] Activation of the EGF receptor has a protective effect against TNF-induced apoptosis. Recent studies have indicated that R-spondin-1 can mitigate inflammation in colitis models characterized by epithelial damage.[178,179]

Inhibition of Intestinal Epithelium Permeability

Lowering intestinal epithelium permeability holds the potential for controlling the progression of inflammation. As mentioned earlier, the phosphorylation of MLC can induce an increase in pericellular permeability regulated by TJs.[36] A novel oligopeptide, PIK, has been reported to inhibit MLCK, resulting in the reversible increase of transepithelial resistance and down-regulation of pericellular permeability.[127] It is noteworthy that various subtypes of MLCK play unique and crucial roles. For instance, the smooth muscle isoform of MLCK is pivotal in intestinal contraction, airway constriction, and blood pressure regulation.[180] However, all MLCK subtypes share the same catalytic domain. Therefore, unless drugs specifically targeting long MLCK are developed, the clinical application of MLCK inhibitors may not be feasible.[6,126]

Furthermore, PIK demonstrates significant efficacy in alleviating mild intestinal permeability defects but falls short in reversing severe damage induced by higher doses of IFN-γ and TNF-α.[127] Additionally, occludin and claudin-2 present

potentially druggable targets.[6] For example, intestinal alkaline phosphatase (IAP) can down-regulate the expression of vascular endothelial growth factor and claudin-2, thereby reducing intestinal permeability.[25]

Mucus Layer Restoration

The restoration of the mucus layer holds the potential to enhance intestinal barrier function. In the remission phase of IBD, increasing dietary fiber intake may reduce microbial consumption of mucins, facilitating the restoration of the mucus layer and thereby extending the remission period.[53] However, during the active phase of IBD, excessive secretion of MUC2 leads to increased ER stress in goblet cells.[53] In such instances, the application of exogenous mucins can be considered to supplement the deficient mucus barrier function, alleviate ER stress, and promote the recovery of goblet cells.[53]

Gut Microbiota Homeostasis

Reestablishing microbiota homeostasis stands out as a promising alternative for IBD therapy, given the crucial role of the gut microbiota in maintaining the integrity of the intestinal barrier.[7,181] SCFAs, protective factors produced by commensal microbiota, decrease during the course of IBD. Studies have indicated that SCFAs can stimulate the differentiation and proliferation of epithelial cells in vivo.[182,183] Therefore, supplementing exogenous SCFAs holds the potential to promote epithelial repair in the treatment of IBD.[182]

Additionally, fecal microbiota transplantation (FMT) represents a straightforward yet effective method for modulating gut microbiota.[53] Research has demonstrated that FMT can rapidly reduce mucosal permeability, improve intestinal barrier integrity, and decrease colonic inflammation. Consequently, FMT can be employed to inhibit the progression of IBD and prevent the recurrence of UC.[184] However, the optimal treatment frequency of FMT and the identification of beneficial bacterial strains require further investigation in future studies.

Molecular Target

Regulating the molecular mechanisms within the cell emerges as a valuable therapeutic strategy worthy of attention. In chronic inflammation associated with IBD, there is a distinct decrease in BRG1 expression. BRG1 has been proposed to function as an autophagy checkpoint linked to colitis, playing a role in maintaining the homeostasis of IECs. However, the deficiency of BRG1 results in impaired autophagy, leading to the production of excessive ROS and compromising barrier integrity.[185] Intriguingly, the antioxidant N-acetyl-L-cysteine (NAC) has been shown to reverse this process partially.[185]

Furthermore, mitochondria constitute another critical therapeutic target in IBD treatment.[186] In IBD patients, there is a decreased expression of PHB1, an abundant inner mitochondrial membrane protein that stabilizes mitochondrial DNA-encoded proteins, regulates mitochondrial fusion, and maintains optimal electron transport chain activity.[187,188] Consequently, PHB1 deficiency leads to loss of viability in the ISC niche and Paneth cell defects.[189] Mitochondria-targeted antioxidants, such as Mito-Tempo or MitoQ, can alleviate this damage.[190,191] During the active phase of UC, the release of mitochondrial DNA into cells serves as a trigger, prompting neutrophils in the peripheral circulation to secrete IL-8 and thereby exacerbating inflammation. Consequently, strategies to prevent the release of mitochondrial DNA present a promising therapeutic avenue for IBD.[186] Treatments that specifically target mitochondria are particularly significant for Paneth cells, where mitochondrial dysfunction precipitates defects in these cells.[186] Given that Paneth cell defects arise before the onset of severe inflammation, they serve as predictive markers for early relapse and molecular indicators of incipient inflammation.[186]

Others

In addition to the previously mentioned treatment strategies, several alternative therapeutic approaches show promise for restoring intestinal epithelial integrity. Early studies suggest that mannose treatment improves lysosomal integrity, reduces the release of cathepsin B, and prevents mitochondrial dysfunction, thereby inhibiting MLCK-induced disruption in colonic inflammation.[192] Amino acids such as arginine, histidine, and glutamine can promote enterocyte proliferation

and reduce mucosal permeability by regulating TJ proteins.[193,194] Matrix metalloproteinases play a role in ECM remodeling, promoting cell migration, and driving the intestinal epithelial regeneration process.[195]

Moreover, the regulation of actin and microtubule cytoskeleton contraction holds the potential for promoting epithelial repair. For example, fidgetin-like 2 (FL2), a microtubule-severing enzyme, promotes successful wound repair in mice by regulating microtubule contraction and organizing the microtubule cytoskeleton.[196] Various actin-remodeling proteins have also been identified as potential new targets for improving wound healing.[165] Additionally, sacral nerve stimulation (SNS) shows promise as a specific therapeutic method by enhancing mucosal barrier function, with case reports supporting its use in treating IBD.[197]

The development of nanosystem targeting technology represents a significant advancement over traditional therapies, offering new perspectives for IBD treatment. The potential of nanozymes in treating IBD has garnered increasing attention. Recent studies have demonstrated that oxidized cerium nanozyme (D-CeO2), CeO2@PDA-PEG, and dopamine nanoparticles coupled with mCRAMP, can effectively clear ROS and alleviate colonic inflammation.[198–201] Additionally, nano-medicines encapsulating antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), have shown promise. Through the co-delivery of CaO2 (a CAT substrate) and dopamine, this nanosystem facilitates CAT-catalyzed oxygen generation and in-situ polymerization of dopamine to form a thin and integrated polydopamine (PDA) coating. Due to the high adhesive properties of PDA, it can cover the intestinal barrier, thereby limiting intestinal leakage and exhibiting a favorable anti-inflammatory effect.[202] These nanoformulations exhibit high biocompatibility and demonstrate inflammatory targeting properties, anti-inflammatory effects, and positive modulation of gut microbiota, offering novel strategies for intervening in and treating colitis.[198–201]

In addition, the colon-targeted quercetin delivery system, COS-CaP-QT, targets the colon via pH-dependent release, regulating Th2 cells and ILC3s proliferation through the Notch pathway and reshaping the inflammatory microenvironment.[203] HA-modified poly lactic-co-glycolic acid nanoparticles exert potent therapeutic effects in UC by modulating intestinal IEC/stem cell regeneration, angiogenesis, and inflammation improvement, leading to transcriptional reprogramming of immune response genes in colonic tissues.[204] Ginger polysaccharides alleviate intestinal inflammation by inhibiting pro-inflammatory cytokine levels to regulate intestinal inflammation, up-regulating occludin-1 and ZO-1, and modulating gut microbiota.[205] Nanocrystalline cellulose effectively treats UC by regulating the MAPK pathway of MUC2 and the relative abundance of Akkermansia and Odoribacter, without causing bodily harm as mucin substitutes.[206] LBL-CO@MPDA specifically accumulates onto positively charged inflamed colon lesions through electrostatic interactions. CO@MPDA improves inflammatory conditions via MPDA-mediated ROS scavenging and CO-mediated immunomodulation. CO delivery activates heme oxygenase-1, leading to macrophage M2 polarization via the Notch/Hes1/Stat3 signaling pathway, while suppressing inflammation by downregulating the p38 MAPK and NF-κB (p50/p65) signaling pathways.[207]

HA holds potential in the treatment of IBD. Research indicates that HA enhances intestinal barrier integrity by increasing epithelial cell adhesion proteins and inhibiting the transcription of inflammatory factors, thereby reducing intestinal permeability.[208] Specifically, HA enema plays a crucial role in suppressing intestinal inflammation, possibly by modulating cell growth and cytoskeletal rearrangement via epithelial cell adhesion signaling (eg, E-cadherin). Additionally, HA enema activates the LXR/RXR pathway, further inhibiting the NF-kB pathway of mucosal inflammation.[208] However, limitations exist in its clinical application, including the lack of specific colitis models and testing in chronic or large animal models.[208] Future investigations should focus on exploring HA's mechanisms in intestinal inflammation and considering its combination with other therapeutic drugs for more effective treatment strategies.[208]

Dietary interventions also play a significant role in the treatment of IBD. Dietary therapy can alleviate IBD through the following four key steps: managing nutritional needs, influencing disease activity, controlling disease complications, and preventing disease in offspring.[209] The Crohn's Disease Exclusion Diet aims to limit harmful dietary components for gut microbiota, though concerns exist about potential long-term negative nutritional and psychosocial effects.[209–211] In contrast, the Specific Carbohydrate Diet reduces inflammation by avoiding specific carbohydrates but may lead to nutritional deficiencies, particularly in calcium intake.[212] The Paleo Auto-Immune Protocol eliminates potentially inflammatory foods, yet its safety is questioned due to lacking nutritional support and high meat consumption.[209,213] On the other hand, the Plant-based diet emphasizes increased prebiotic intake for beneficial gut bacteria and is relatively

safer, reducing the risk of nutritional inadequacies.[209,214] The Mediterranean diet, with its anti-inflammatory properties from plant-based foods, aligns with healthy eating guidelines and is generally safer.[212]

While other approaches like CD-TREAT, low-sulfur diet, low-emulsifier or carrageenan diets, low-fat diet, low-meat diet, and Novel UC exclusion diet offer unique features, uncertainties remain regarding their safety and nutritional support.[209,215–219] Therefore, selecting an appropriate dietary therapy should consider its characteristics, safety, and impact on nutritional intake to achieve the best treatment outcomes.

Finally, recent scientific studies have reported several alternative treatments for IBD, including ZINC40099027 (ZN27), phosphatidylcholine (LT-02), the PDE4 inhibitors Apremilast, Mongersen GED0301, STNM01, Alicaforsen, Momordica charantia (MCh), and others.[220–223] While these approaches collectively propose numerous promising therapeutic strategies for IBD treatment, as of now, specific targeted drugs have not yet been discovered (Table 2).

Table 2 Methods and Their Specific Principles for Restoring Intestinal Barrier

Treatment Method	Treatment Approach	Key Aspects and Effects
Stem Cells Transplantation	Engraftment of ISC	Limited therapeutic effect when damaging factors exist.
	Transplantation of MSCs and HSCs	Proven effectiveness.
	Culture and transplantation of organoids	Accelerates healing of inflamed mucosa.
	Healing cytokines	EGF and R-spondin-1 promote self-repair and protect against TNF-induced apoptosis.
Inhibition of intestinal epithelium permeability	Inhibition with PIK	PIK inhibits MLC kinase, increasing transepithelial resistance and down-regulating pericellular permeability.
		Limitation: Unique roles of MLCK subtypes, requiring specific drug targeting.
	Targeting occludin and claudin-2	IAP reduces intestinal permeability by down-regulating expression of vascular endothelial growth factor and claudin-2.
Mucus layer restoration	Dietary fiber intake during remission	Reduces microbial consumption of mucins, promoting mucus layer restoration.
	Exogenous mucins during active phase	Supplements deficient mucus barrier function, alleviates ER stress, and promotes recovery of goblet cells.
Gut microbiota homeostasis	Supplementing SCFAs	SCFAs stimulate differentiation and proliferation of epithelial cells.
	Fecal microbiota transplantation (FMT)	Effectively reduces mucosal permeability, improves intestinal barrier integrity, and reduces colonic inflammation.
Molecular target regulation	Increasing BRG1 expression	BRG1 serves as an autophagy checkpoint associated with colitis.
		Antioxidant NAC partially reverses impaired autophagy.
	Targeting mitochondria	Mitochondria-targeted antioxidants (Mito-Tempo, MitoQ) alleviate damage caused by PHB1 deficiency. - Preventing release of mitochondrial DNA is a promising approach.
Other therapeutic approaches	Mannose treatment	Improves lysosomal integrity, reduces release of cathepsin B, and inhibits MLCK-induced disruption.
	Amino acids (arginine, histidine, glutamine)	Promote enterocyte proliferation, reduce mucosal permeability by regulating TJ proteins.
	Matrix metalloproteinases	Regulate extracellular matrix remodeling, promote cell migration, and drive intestinal epithelial regeneration.
	Regulation of actin and microtubule	FL2 promotes successful wound repair by regulating microtubule contraction and organizing the microtubule cytoskeleton.
	Sacral nerve stimulation (SNS)	Enhances mucosal barrier function. - Case reports indicate potential use in treating IBD.
General note	Various alternative treatments	ZINC40099027 (ZN27), phosphatidylcholine (LT-02), PDE4 inhibitor Apremilast, Mongersen GED0301, STNM01, Alicaforsen, Momordica charantia (MCh), etc.

Abbreviations: ISC, intestinal stem cells; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; PIK, membrane permeant inhibitor of MLC kinase; SCFAs, short-chain fatty acids; FMT, Fecal microbiota transplantation; SNS, Sacral nerve stimulation; EGF, epidermal growth factor; MLCK, myosin light chain kinase; IAP, intestinal alkaline phosphatase; BRG1, Brahma-related gene1; NAC, N-acetyl-L-cysteine; PHB1, Prohibitin 1; TJ, tight junction; FL2, fidgetin-like 2; IBD, inflammatory bowel disease; ZN27, ZINC40099027; LT-02, phosphatidylcholine; PDE, Phosphodiesterase-4; MCh, Momordica charantia.

Conclusion and Perspectives

This review initiates by scrutinizing the components and mechanisms of the intestinal barrier, covering the epithelium, cell junctions, mucus layer, and the self-repair capacity of the intestine. Next, we explore the vicious cycle created by dysfunction of these defenders in IBD. Finally, we provide an overview of therapeutic strategies and targets for restoring intestinal barrier integrity (Table 3. Comparison of Different Therapies).

Previous studies have highlighted the negative side effects of non-targeted therapies, particularly immunosuppressive agents. However, technological advancements and a deeper understanding of IBD inflammation and intestinal self-repair have revealed new therapeutic targets for restoring epithelial integrity. Recent research has identified targets in the crosstalk between IEC death and the immune response, including ISC proliferation and differentiation, stem cell transplantation, and organoid culture. While growth factors are used for short bowel syndrome, their application in IBD remains unexplored.[15] Restoring cell junction and mucus layer function, regulating the immune system, and

Table 3 Comparision of Different Therapies

Therapy	Strengths	Weaknesses
Stem Cell Transplantation	Promotes proliferation and differentiation of ISCs Effective in some clinical trials Potential for autologous transplantation	Severe adverse events Risk of malignant transformation Requires further research on immunomodulatory properties Risk of cancer
Organoid Culture	Mimics intestinal epithelium structure Can be expanded in vitro Potential for gene editing	Limited by severe epithelial damage Challenges in identifying optimal clinical outcomes Retains epigenetic features
Growth Factors (eg, EGF, R-spondin-1)	Promotes epithelial growth Mitigates inflammation in colitis models	Risk of cancer Not yet explored for IBD in clinical applications
Molecular Targets (eg, MLCK inhibitors, BRG1)	Potential to reduce intestinal permeability Antioxidants can mitigate damage	No specific MLCK inhibitors available Partial efficacy in severe cases
Microbial Metabolites (eg, tryptophan)	Enhances gut barrier integrity Promising in reducing intestinal permeability	Variation in individual microbiota Requires further study on human concentrations and mechanisms
Polysaccharide Nanoparticles	Navigates mucus layer Controlled drug release Enhances therapeutic efficacy	Complex composition Challenges in simulating IBD conditions Issues with encapsulation efficiency
AI and Big Data Analytics	Identifies complex disease patterns Enhances precision of drug development Predicts treatment outcomes	Requires extensive dat Dependent on algorithm accuracy
Gut Microbiota Homeostasis (eg, FMT, SCFAs)	Rapidly reduces mucosal permeability Improves barrier integrity Decreases inflammation	Requires further investigation for optimal treatment frequency Need to identify beneficial bacterial strains
Mucus Layer Restoration	Enhances barrier function Reduces microbial consumption of mucins	Exogenous mucins needed during active IBD ER stress in goblet cells
Dietary Interventions	Influences disease activity Manages nutritional needs Can prevent disease complications Prevent disease in offspring	Need for careful selection based on individual requirements
Nanozymes	High biocompatibility Targets inflammation Modulates gut microbiota	Challenges in precise targeting Requires further research on long-term effects

Abbreviations: EGF, epidermal growth factor; BRG1, Brahma-related gene1; FMT, fecal microbiota transplantation; SCFAs, short-chain fatty acids; ISC, intestinal stem cells; IBD, inflammatory bowel disease; MLCK, myosin light chain kinase; ER, endoplasmic reticulum.

rebuilding the intestinal microbiota are also promising approaches. Treatments targeting molecular mechanisms, such as blocking MLCK, show potential for IBD therapy.

While restoring the barrier integrity is an ideal option for IBD, its clinical application faces unresolved issues. Hematopoietic stem cell transplantation (HSCT) has shown certain efficacy in treating IBD in clinical trials. However, the occurrence of frequent severe adverse events has sparked a controversial debate on whether HSCT can be considered an alternative treatment for IBD.[224] Screening for gene mutations associated with colorectal cancer is deemed necessary during the isolation of ISCs in IBD therapy due to an increased risk of post-transplantation malignant transformation.[174] Injection of embryonic stem cell-derived MSCs derived from fetal sources can alleviate intestinal inflammation by increasing IGF-1 levels, upregulating IGF1R-PI3K-AKT expression, promoting cell proliferation, and reducing apoptosis.[225] However, the therapeutic mechanism requires further clarification, particularly regarding its immunomodulatory properties. Additionally, MSCs derived from embryonic stem cells may face challenges in large-scale cultivation and production.[225]

Stem cells hold great promise in the treatment of IBD, particularly through the study of the intricate and complex interactions between stem cells and immune cells.[174] Past research has shown that T cells and ILCs significantly impact the fate and function of stem cells. Additionally, cytokines can directly promote or restrict the proliferation, differentiation, and apoptosis of stem cells, making them crucial mediators in maintaining or disrupting the intestinal epithelial barrier.[85,174] However, the interaction between stem cells and immune cells is highly complex, requiring further in-depth research.[174] Considering the connections between stem cells and immune cells, the integration of biologic agents and stem cell transplantation may revolutionize the future treatment of IBD patients.[174]

Gene editing holds the potential to correct genetic defects in organoids, contributing to the high sensitivity of IBD.[226] However, uncertainties persist regarding the precise identification of these defects and whether edited organoids can withstand future IBD-related damage.[168,226] Evidence suggests that, despite significant plasticity, transplanted tissues may retain epigenetic features of their original tissue source.[227] In vitro culture protocols for ISCs also require further refinement to maximize ISC yield.[228] In the clinical realm, optimal indicators for evaluating the clinical outcomes of organoid transplantation remain uncertain, and it's undetermined which types of IBD patients would derive the greatest benefits from these therapies.[174] Additional clinical data collection is imperative.[174] Notably, in some patients, the severity of the original damage to the epithelium may hinder the establishment of robust organoid cultures, necessitating alternative treatment approaches.[168] Nonetheless, other therapeutic strategies also confront challenges preventing their clinical application. For instance, EGF and R-spondin-1 can reduce TNF-induced cell apoptosis by activating the Wnt pathway, though this may also contribute to cancer.[6] Moreover, since a specific drug targeting MLCK has not yet emerged, MLCK inhibitors also cannot be used in clinical applications.

Recent research has highlighted the current challenges in repairing the intestinal barrier through various mechanisms and outlined promising future directions for development. Microbial tryptophan metabolites show great promise in treating IBD, though they come with challenges.[229] Studies indicate that metabolites like IEt, IPyA, and I3A enhance gut barrier integrity by acting through the aryl hydrocarbon receptor (AhR), inhibiting actin-regulating proteins MyoIIA and ezrin, thereby reducing intestinal permeability.[229] However, the exact concentrations and mechanisms of these metabolites in humans need further study. The variation in gut microbiota among individuals also affects metabolite production.[229] While AhR's role is crucial, the effects on different immune cells and pathways require more research. Future research should focus on understanding these metabolites' mechanisms, personalizing treatments based on individual microbiota differences, and developing accurate human disease models, such as patient-derived organoids, to better study IBD.[229]

Polysaccharide nanoparticulate drug delivery systems show promise in treating IBD, overcoming the adverse effects associated with traditional targeted therapies.[207] These nanoparticles can navigate through the mucus layer, adhere to inflamed areas as a protective layer, and release drugs in a controlled manner, enhancing therapeutic efficacy.[230] However, several challenges persist in polysaccharide-based drug delivery. Polysaccharides are complex, varying in composition due to extraction conditions. Improved in vitro methods are needed to accurately simulate IBD conditions.[230] Animal IBD models inadequately represent human IBD, necessitating more precise alternatives.[230] Additionally, issues such as low encapsulation efficiency and premature drug release need addressing through

strategies like smart-responsive drug-polysaccharide conjugates.[230] Future research should focus on refining production methods, exploring new drug targets, and developing smart-responsive systems for targeted drug delivery in IBD treatment.[230]

The advancement of artificial intelligence (AI) offers a new perspective for developing IBD therapies. By employing computational algorithms to analyze vast datasets such as transcriptomics, AI constructs gene co-expression networks (GCNs) to unravel the complexity of human diseases, aiding in the prioritization and validation of treatment targets.[231] These networks simplify intricate multi-cellular processes, identifying patterns beyond human analysis and thereby enhancing prediction accuracy. AI can simulate the progression of complex diseases like IBD, improving the precision of drug development.[231] Looking ahead, With continuous advancements in AI technology and the ongoing integration of big data analytics, researchers can anticipate more accurate predictions, new target discoveries, and improved treatment outcomes.[231]

Therefore, despite the appeal of restoring barrier integrity as a therapy, implementing these treatments in clinical practice requires further research into the underlying pathogenesis of IBD, particularly the causative relationships among different dysfunctions. Additionally, a comprehensive understanding of the mechanisms behind these therapeutic strategies is necessary to identify and minimize potential side effects.

Abbreviations

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IECs, intestinal epithelial cells; M cells, microfold cells; EECs, enteroendocrine cells; AMPs, antimicrobial peptides; TJ, tight junction; AJ, adherens junction; JAM, junctional adhesion molecule; MLC, myosin regulatory light chain; MLCK1, myosin light chain kinase 1; ZO, Zonula Occludens; E-cadherins, epithelial cadherins; MUC2, mucin-2; FCGBP, Fcγ binding protein; CLCA1, calcium-activated chloride channel regulator1; NHE3, Na+/H+ exchanger 3; ISCs, intestinal stem cells; IL, Interleukin; Grem1, Gremlin 1; Rspo1, R-spondin 1; Wnt2b, Recombinant Wingless Type MMTV Integration Site Family, Member 2B; EGCs, Enteric glial cells; proEGF, pro epidermal growth factor; EGF, epidermal growth factor; YAP, Yes-associated protein; TAZ, Tafazzin; STAT3, Signal Transducer and Activator of Transcription 3; ILCs, innate lymphoid cells; CBCs, Crypt Base Columnar Cells; CREB, cAMP response element-binding protein; WISP-1, WNT1-inducible signaling protein 1; DAMPs, Damage-Associated Molecular Patterns; SETDB, SET domain, bifurcated; ZBP1, Z-DNA binding protein 1; TNVs, turmeric-derived nanovesicles; PGE2, PGE2 prostaglandin E2; EP2, Prostaglandin E2 receptor 2; XBP1, Recombinant X-Box Binding Protein 1; PHB1, Prohibitin 1; Hsp60, Heat Shock Protein 60; DCA, Dichloroacetate; TNF-α, Tumor Necrosis Factor-α; IFN-γ, interferon-γ; Th2, T helper 2 cell; WFDC2, Recombinant WAP Four Disulfide Core Domain Protein 2; ER, endoplasmic reticulum; GI tract, Gastrointestinal tract; TGF-β, transforming growth factor β; Treg, regulatory T cell; SCFAs, short-chain fatty acids; SYNPO, actin-binding protein synaptopodin; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; PIK, membrane permeant inhibitor of MLC kinase; IAP, intestinal alkaline phosphatase; FMT, fecal microbiota transplantation; BRG1, Brahma-related gene 1; ROS, reactive oxygen species; NAC, N-acetyl-L-cysteine; MitoQ, Mitochondrial-targeted coenzyme Q10; FL2, fidgetin-like 2; SOD, Superoxide Dismutase; CAT, Catalase; PDA, polydopamine; ZN27, ZINC40099027; PDE4, Phosphodiesterase-4; SNS, sacral nerve stimulation; MCh, Momordica charantia; HSCT, Hematopoietic stem cell transplantation; HA, Hyaluronic acid; GCNs, gene co-expression networks; AI, Artificial intelligence.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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