Review

Intestinal Barrier: Mechanisms of Disruption and Strategies for Restoration in Ulcerative Colitis

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Intestinal Barrier: Mechanisms of Disruption and Strategies for Restoration in Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) is a chronic, relapsing-remitting subtype of inflammatory bowel disease (IBD), featured by continuous mucosal inflammation restricted to the colon and rectum. Although the exact pathogenesis of UC has not been fully clarified, intestinal barrier impairment and disrupted mucosal homeostasis are recognized as the central mechanism. Therefore, restoring intestinal mucosal barrier function represents a core strategy for UC prevention and treatment, which aligns with the therapeutic goal of achieving mucosal healing and sustained remission. In this review, we outline the composition and functional significance of the intestinal barrier, explore key mechanisms underlying its disruption, and summarize recent advances in UC-related monitoring strategies. Finally, we explore novel therapeutic approaches aimed at epithelial barrier repair. The review aims to provide insights valuable for both basic research and clinical management of UC.

Keywords: intestinal barrier; monitoring and therapeutic strategies; ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is a chronic, relapsing-remitting inflammatory bowel disease (IBD) characterized by continuous mucosal inflammation confined to the colon and rectum, and its incidence has risen rapidly in newly industrialized countries in Asia, Latin America, and the Middle East[1], imposing a substantial burden on healthcare systems and severely compromising patients' long-term quality of life.

The pathogenesis of UC remains incompletely elucidated, with numerous studies focusing on immune-inflammatory cascades and dysregulated host-microbe interactions. However, the initiation of disease pathogenesis is fundamentally driven by impairment of the intestinal barrier and breakdown of mucosal homeostasis[2,3]. Accumulating evidence indicates that intestinal barrier dysfunction may precede the clinical confirmation of IBD by several years[4,5]. Under physiological conditions with an intact mucosal layer, only a limited number of luminal antigens can translocate into the lamina propria; in contrast, disruption of this mucosal barrier permits excessive luminal antigen penetration, which in turn facilitates massive immune cell infiltration and exacerbates the inflammatory cascade[6]. Overall, the impairment of intestinal mucosal barrier function represents a core mechanism underlying the pathogenesis of UC, highlighting that targeting key regulatory pathways and repairing the damaged barrier are critical for the effective prevention and treatment of this disease. The primary objective of current UC therapeutic strategies is to achieve mucosal healing and durable remission, thereby reducing hospitalization rates and the need for bowel resection[5].

This article reviews the composition and functional characteristics of the intestinal mucosal barrier, analyzes the underlying mechanisms of its disruption in UC, summarizes recent advances in the development of novel monitoring strategies and therapeutic targets for UC related to the

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intestinal barrier, and discusses future research directions, aiming to provide a reference for basic research and clinical practice of UC.

2. Composition and Function of the Intestinal Barrier

The intestinal barrier is an intricate multi-layered structure consisting of epithelial, microbial, biochemical, and immunological elements (Figure 1), which act synergistically to exert their integrated functions[7].

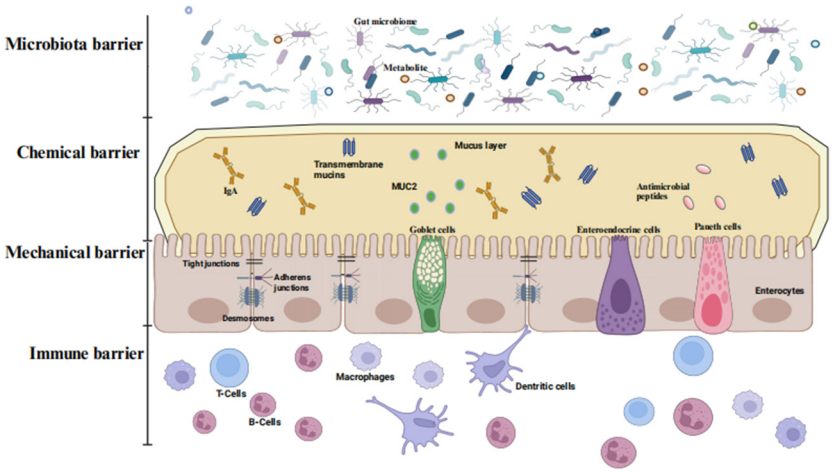

Figure 1. Diagram of the intestinal barrier structure.

The epithelial cell layer, constituting the physical barrier, serves as the central structural and functional core of the intestinal barrier. It encompasses a heterogeneous population of cells such as enterocytes, enteroendocrine cells, goblet cells, Paneth cells, tuft cells, and microfold cells[7], all of which originate from pluripotent intestinal stem cells localized in the intestinal crypts[8]. These stem cells undergo directed differentiation to produce the specialized cell types that collectively maintain intestinal barrier integrity. The epithelial cell layer is a highly dynamic structure, which is characterized by rapid self-renewal, with the entire epithelial layer estimated to be fully replaced every 4–7 days[9].

Intestinal epithelial cells are closely interconnected by junctional complexes that consist of tight junctions, adherens junctions and desmosomes[10], with tight junctions being recognized as the core regulators governing intestinal paracellular transport (Figure 1)[11]. This specialized structural arrangement enables the selective permeation of ions and other bioactive substances, while exerting an effective barrier function against the translocation of harmful molecules including bacterial toxins. Tight junctions are assembled from claudins, occludin, MARVEL domain-containing protein 2 (tricellulin), junctional adhesion molecules, and zonula occludens proteins. The claudin superfamily can be categorized into two subgroups: barrier-forming or sealing claudins (including claudin-1/3/4/5/7/8/12), which are recognized as structural components of tight junctions, and pore-forming claudins (including claudin-2/10/15/17)[12]. Claudins are key mediators in the formation of paracellular barriers or channels, where they control the flux of ions and water through epithelial and endothelial tissues. Variations in claudin interactions induce structural modifications to these channels, leading to altered tight junctions permeability toward ions and macromolecules. Specifically, claudin-23 not only modulates tight junctions' paracellular permeability significantly but also recruits claudin-3 and claudin-4, two prototypical barrier-forming claudins—to regulate tight junctions' structure and their associated barrier function[13]. IBD is typically manifested with impaired barrier integrity and enhanced intestinal permeability, accompanied by the downregulated expression of sealing claudins alongside the upregulated expression of pore-forming claudins[14].

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The intestinal epithelial cells are coated by a mucus layer; this mucus layer in the large intestine is composed of two layers, the inner, firm mucus layer and the outer, loose mucus layer. These mucus layers are organized by gel-forming MUC2, which is synthesized and secreted by goblet cells[8,15]. In addition to these secreted mucins, transmembrane mucins are also present in the mucus layer, where they perform dual functions of intestinal barrier maintenance and cellular signaling. This mucus layer, whose stability is supported by Paneth cell-derived antimicrobial peptides, not only acts as a critical barrier against direct contact between epithelial cells and the dense microbial population, but also exerts a targeted immunomodulatory effect by conveying tolerogenic signals to constrain the immunogenicity of luminal antigens[16]—defects in this protective system constitute a core characteristic of colitis[17]. Besides mucins, antimicrobial peptides including defensins and lysozyme, as well as secretory IgA (sIgA), participate in maintaining intestinal chemical barrier integrity via neutralizing or eradicating invading pathogens[18].

The intestinal biological barrier commonly refers to the intestinal microbiota, which is composed of trillions of distinct microorganisms. As a core regulator of intestinal homeostasis, the gut microbiota contributes to intestinal barrier formation, boosts mucosal immune reactivity, and preserves the equilibrium of the intestinal milieu[19]. Individuals suffering from UC experience gut microbiota dysbiosis, which is characterized by a reduction in bacterial diversity, particularly in areas with active inflammation[19].

The intestinal immune barrier is primarily formed by gut-associated lymphoid tissue (GALT), which mainly comprises aggregated lymphoid nodules (ALNs), intraepithelial lymphocytes (IELs), and lamina propria lymphocytes (LPLs) (Figure 1)[20,21]. In addition to identifying and eradicating pathogenic microorganisms, dietary antigens, and other harmful luminal contents, this barrier also mediates immune tolerance toward commensal gut microbiota[22].

The physical and chemical barriers constitute the central elements of the four intestinal barriers[18], whose coordinated interactions sustain intestinal microenvironmental homeostasis, whereas impaired interaction between them may induce the development of UC[20].

3. Mechanisms of Impaired Intestinal Barrier Function in UC

3.1. Genetic Susceptibility

IBD is a multifactorial disorder driven by the interplay between genetic predisposition and environmental exposures. Currently, numerous large genome-wide association studies (GWAS) have successfully uncovered over 200 variants implicated in IBD genetic susceptibility[23]. The majority of these variants are intergenic and confer merely modest genetic risk, and the identified loci together contribute to some 20-30% of total genetic susceptibility[24]. These GWAS analyses have identified key components of several pathways that underpin IBD susceptibility, most of which are involved in innate immunity, T cell signaling, and intestinal barrier function[23].

Studies of rare variants in familial IBD and very early-onset colitis patients have identified genetic variants with significantly larger effect sizes. In a multigenerational family from South Asia, all members carrying the A143T mutation in the *OTUD3* gene developed refractory UC. Both mouse models and human colonic organoids show that *OTUD3* gene abnormalities may result in aberrant tight junction protein Zonula Occludens-1 (ZO-1) and increased intestinal permeability. Additionally, the increased intestinal permeability preceded the onset of colitis symptoms, even earlier than immune cell infiltration or histological colitis in mouse model. This evidence indicates that *OTUD3* gene is a critical regulator of intestinal barrier function by maintaining the normal function of the tight junction protein ZO-1. Its dysregulation leads to intestinal barrier hyperpermeability, accompanied by elevated levels of pro-inflammatory cytokines (IL-8), ultimately precipitating colitis[25].

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3.2. Cytokine-Mediated Intestinal Barrier Integrity Regulation

Tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) have been identified as two of the most well-characterized proinflammatory cytokines with respect to their modulatory effects on the intestinal tight junction barrier[26,27]. Specifically, these inflammatory mediators significantly upregulate myosin light-chain kinase (MLCK) protein expression, and this in turn markedly increased the phosphorylation of myosin II regulatory light chain (MLC). As the direct mediator of tight junction disruption, MLC phosphorylation resulted in the disorganization and redistribution of ZO-1, Occludin, and Claudin-1, indicative of tight junction structural damage and consequently impaired intestinal barrier integrity[28].

Strikingly, targeting TNF not only suppresses inflammation but also promotes effective tissue repair in a subset of IBD patients[29]. Furthermore, a recently established humanized experimental colitis model revealed that TNF impairs mucosal healing by upregulating IL-22BP, a soluble endogenous antagonist of IL-22 in the colonic mucosa, thereby disrupting IL-22/STAT3-mediated mucosal restitution during colitis progression[30]. It is well established that IL-22 exerts dual protective effects on the intestinal mucosa through STAT3 activation: it promotes the expression of genes associated with mucin production, epithelial proliferation, regeneration, and wound healing to attenuate inflammation[31], while also increasing Paneth cell abundance and the expression of antimicrobial peptides in enterocytes, goblet cells, and Paneth cells[32].

3.3. Modulator of Intestinal Tight Junctions

Zonula occludens toxin (Zot), a type of enterotoxin, can open intercellular tight junctions, and thus participates in the modulation of the paracellular transport pathway. This toxin induces actin polymerization in target cells, which in turn triggers the disassembly of tight junction protein complexes via a protein kinase C (PKC)- dependent signaling pathway. Accumulating research evidence has demonstrated that human zonulin, an endogenous homolog of Zot in humans, exerts a conserved mechanism of action by binding to the same apical receptor on intestinal epithelial cells, thereby modulating tight junction permeability[33]. Triggered by gliadin specific peptides or bacterial pathogens via a signaling cascade that is CXCR3-mediated and MyD88-dependent, zonulin then transactivates the epidermal growth factor receptor (EGFR) through protease-activated receptor 2 (PAR2), which in turn initiates PKCα-dependent disassembly of epithelial tight junctions. The resulting increase in intestinal permeability facilitates the paracellular translocation of non-self antigens into the lamina propria, where these antigens gain access to and interact with the host immune system, thereby triggering subsequent immune responses[34]. Zonulin is the only modulator that exerts a physiological effect on intestinal permeability to be identified in published research[35].

Findings revealed markedly elevated serum zonulin concentrations in patients with UC, and serum zonulin concentrations were found to be inversely correlated with disease duration. Notably, no significant differences were observed between patients with Crohn's Disease and UC. But serum zonulin levels enabled the discrimination of IBD patients from healthy controls with high diagnostic accuracy, thereby validating that zonulin levels may serve as a potential biomarker for predicting disease onset and progression[36]. A study has confirmed that intestinal barrier impairment emerges prior to the inflammatory stage of autoimmune arthritis in both murine experimental models and human clinical cohorts. Notably, zonulin acts as a pivotal driver of this pathological cascade: it disrupts intestinal tight junction proteins, elevates intestinal permeability, and facilitates the infiltration of Th1/Th17 cells into the lamina propria—all of these events occur before the onset of arthritis in both human patients and murine models[37].

3.4. Gut Microbiota and Its Derived Metabolites

As a pivotal bridge connecting the gut microbiota and host signal transduction, gut microbiota-derived metabolites exert irreplaceable regulatory effects on intestinal homeostasis. Among the

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diverse array of gut microbiota-derived metabolites, short-chain fatty acids (SCFAs), tryptophan catabolites, and secondary bile acids (SBAs) stand out as three representative classes of bioactive molecules, whose homeostatic balance is critical for sustaining intestinal immune tolerance and mucosal integrity.

Bacteroidetes and *Firmicutes* are the most abundant commensal microbes in the intestine[38]. Commensal microbes in the distal gut metabolize indigestible substrates to produce SCFAs. The major SCFAs include formate, acetate, propionate, and butyrate[39]; *Bacteroidetes* mainly produce acetic acid and propionic acid, while *Firmicutes* mainly produce butyrate in the human intestine[40]. Among these metabolites, butyrate is recognized as the most preferred energy source to sustain the metabolic activity of intestinal epithelial cells (IECs)[41], and plays a pivotal role in maintaining the structural integrity of the intestinal epithelial barrier as well as the functional homeostasis of host immune systems.The capacity of butyrate to preserve intestinal epithelial barrier integrity stems from both direct and indirect regulatory pathways. Directly, butyrate can maintain the proliferation of small intestinal epithelial cells and induce the transcription of genes encoding tight junction components[39]. Indirectly, butyrate exerts immunomodulatory and anti-inflammatory effects on lymphoid cells and $CD4^+$T cells, which in turn modulate intestinal epithelial barrier function. Notably, butyrate drives the release of IL-22 in these two cell types. As a key cytokine, IL-22 plays a pivotal role in sustaining intestinal immune homeostasis and reinforcing the structural integrity of the intestinal epithelial barrier[42], as noted above.

Alterations in gut microbial composition characterized by reduced abundance of butyrate-producing bacteria such as *Roseburia* spp. are strongly associated with UC[43]. Such shifts in microbiota, together with diets deficient in resistant starch, lead to decreased butyrate levels, which in turn can compromise the structural integrity of the intestinal epithelial barrier[44].

Tryptophan, a necessary amino acid, plays an important role in regulating physiological functions and disease progression through the following three metabolic pathways: approximately 1-2% tryptophan is converted into serotonin (5-HT) in host cells[45]; about 4-6% is directly degraded by gut microbiota in the intestine to produce various indole derivatives such as indole-3-propionic acid (IPA), indoleacetic acid (IAA), indoxyl sulfate, and tryptamine[46]; and nearly 95% is catabolized via the kynurenine pathway, primarily in the liver, forming kynurenine and its downstream metabolites[45]. Dysregulated tryptophan metabolism, partially driven by gut microbial dysbiosis, correlates with compromised intestinal epithelial barrier integrity, aberrant immune activation, and disrupted mucosal tolerance—key pathological hallmarks of IBD[47]. Many indole derivatives produced by gut microbiota serve as ligands for the aryl hydrocarbon receptor (AhR). Activation of AhR is crucial for maintaining intestinal homeostasis and epithelial barrier integrity, as well as regulating immune cells[48]. Both the levels of AhR ligands and AhR expression are frequently diminished in patients with IBD[49]. Previous studies have demonstrated that Lactobacillus KLDS 1.0386, which exhibits high tryptophan-metabolic activity, combined with tryptophan can upregulate the mRNA expression levels of the tight junction protein ZO-1 as well as the mucins MUC1 and MUC2[50]. IPA, produced by *Clostridium sporogenes*, acts as a ligand to activate the pregnane X receptor (PXR) in intestinal epithelial cells. Activated PXR negatively regulates the expression and signaling of Toll-like receptor 4 (TLR4), thereby attenuating pro-inflammatory responses and preserving the integrity of intestinal epithelial structures including tight junctions[46].

SBAs are some of the most concentrated bacterially derived gut metabolites. They are primarily produced by the gut microbiome through modifications of primary bile acids[51]. In turn, altered bile acid profiles are capable of modifying the structure and abundance of intestinal microbial populations[52]. Patients with UC generally have disorders in SBAs metabolism, which is characterized by significantly lower abundances of SBAs, particularly deoxycholic acid (DCA) and lithocholic acid (LCA), compared to healthy controls[53,54], with their abundances positively correlated with *Roseburia*, *Clostridium IV*, *Butyricicoccus* and *Faecalibacterium*[53]. Furthermore, exogenous supplementation of these two bile acids has been proven to alleviate inflammatory damage in a classic dextran sodium sulfate (DSS)-induced colitis model[55]. The protective effect of

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SBAs is primarily achieved through activating the TGR5 receptor, thereby promoting intestinal stem cell proliferation and epithelial regeneration[56], as well as modulating immune cell functions and inhibiting apoptosis in intestinal epithelial cells[57]. Bile acid profiling alterations may also modulate the expression of tight junction proteins, thereby altering intestinal mucosal permeability and impairing barrier integrity[58]. However, chronic DCA supplementation for 24 weeks, which mimics a Western-diet-like high-DCA microenvironment, triggers persistent intestinal inflammation[59], suggesting a dual and context-dependent role of DCA in IBD.

3.5. Autophagic Dysfunction

Autophagy, also termed macroautophagy, is a cellular catabolic process characterized by lysosome-dependent recycling of impaired organelles and aggregated proteins, together with the clearance of intracellular microbial pathogens. Autophagy plays pivotal roles in maintaining intestinal homeostasis and mediating tissue repair, supporting the functional integrity of the intestinal barrier during cellular stress through tight junction modulation and the mitigation of cell death[60].

Multiple autophagy-inducing approaches, such as nutrient starvation, promote clathrin-mediated endocytosis of claudin-2. This process is mediated by adaptor related protein complex 2 subunit Mu 1 (AP2M1), which bridges claudin-2 to clathrin and microtubule associated protein 1 light chain 3 (LC3), leading to ATG7/ATG16L1-dependent autophagic degradation. Consequently, claudin-2 clearance reduces paracellular permeability and enhances barrier function. Conversely, autophagic deficiency (e.g., ATG7 knockout) elevates claudin-2 levels and increases colitis susceptibility[61]. TNF-induced autophagy repression enhances claudin-2 abundance, leading to the dysfunction of epithelial tight junctions and a subsequent increase in intestinal barrier permeability[62]. Src kinase phosphorylates PEAK1 at Y724, enhancing its binding to ZO-1. This interaction masks ZO-1's LC3-interacting region, preventing LC3B recognition and subsequent autophagic degradation, thereby preserving tight junction stability[63].

Intestinal barrier damage induced by a high-fat diet (HFD) is tightly associated with impaired autophagic function; specifically, HFD suppresses autophagy in intestinal epithelial cells, which in turn reduces the expression of tight junction proteins including claudin-1 and claudin-5, diminishes goblet cell counts, disrupts intestinal barrier architecture, and elevates intestinal permeability. Conversely, butyrate treatment markedly upregulates autophagy-related proteins (Beclin-1, ATG7, ATG5). This effectively reverses HFD-induced barrier impairment by restoring tight junction expression, re-establishing epithelial junction integrity, increasing goblet cell populations, strengthening the mucus protective layer, and ultimately reducing permeability[64].

3.6. Aberrant MUC2 Synthesis and Function

MUC2, primarily derived from goblet cells, is a core component of the intestinal mucus barrier. Its biosynthesis and secretion involve a complex process: dimer formation in the endoplasmic reticulum (ER), O-glycosylation and sulfation in the Golgi apparatus, and trimer network formation in the trans-Golgi network[65].

Multiple studies have reported decreased goblet cell count and MUC2 expression[66], as well as reduced levels of MUC2 O-glycosylation and sulfation in IBD[67]. Differentiation of goblet cells is dependent on mitochondrial oxidative phosphorylation (OXPHOS). In UC, loss of p32, which is a key regulator of OXPHOS, causes abnormal goblet cell differentiation and underlies the reduction in goblet cell numbers[68]. Defects in protein synthesis and maturation can trigger the buildup of unfolded or misfolded polypeptides within the ER, thereby activating ER stress responses[69]. Sustained ER stress in turn exacerbates aberrations in MUC2 production, further impairing its subsequent glycosylation and sulfation modifications that typically occur in the Golgi apparatus, and resulting in additional functional deficits of this key mucin. In UC, the O-glycosylation profile of MUC2 is markedly disrupted, characterized by overall reduced glycosylation, truncated glycan chains, and dysfunctional GalNAc-Ts enzymes. As sulfation relies on intact glycan structures, this

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process is also compromised[67]. Furthermore, ER stress-associated misfolding or impaired intracellular transport of MUC2 interferes with its proteolytic maturation and extracellular release, ultimately undermining the integrity of the intestinal mucosal barrier[70]. Fucosyltransferase 8 (FUT8) is the sole enzyme responsible for adding core fucose (α1,6-linkage) to N-glycans. Elevated FUT8 expression is a key feature of UC. Fucosylation alters mucus properties, making it more prone to bacterial entrapment and facilitating bacterial penetration, thereby exacerbating inflammation[71].

The mechanisms responsible for compromising the intestinal mucosal barrier in UC are not independent events, but rather constitute a highly integrated pathological network. Genetic predispositions impair mucosal barrier integrity, increasing its susceptibility to environmental insults. Damaged barrier function allows enhanced infiltration of microbial antigens, triggering aberrant immune responses. Together, these events form a vicious cycle that sustains chronic inflammation and cytokine overproduction, thereby worsening disease severity.

4. Disease Monitoring

The treatment goal of UC should be clinical and endoscopic healing, necessitating close monitoring that goes beyond clinical symptoms. Colonoscopy is widely regarded as the gold standard for disease surveillance, given its ability to assess endoscopic healing status and facilitate biopsy collection for histologic analysis[72,73]. But the invasive nature of colonoscopy compromises patient adherence and limits its application for short-term follow-ups. Consequently, a variety of non-invasive monitoring tools have been developed and validated to complement colonoscopy, enabling more frequent, convenient, and patient-friendly disease assessment.

4.1. Faecal Biomarkers in Monitoring Remission in UC

Prognostication is crucial in ulcerative colitis management, and clinical evidence confirms that inflammatory biomarkers such as fecal calprotectin (FC) and fecal lactoferrin (FL) are essential for this assessment.

Lactoferrin, an 80 kDa iron-chelating glycoprotein, constitutes a major component of the secondary granules present in polymorphonuclear neutrophils (PMNs)[74]. In cases of intestinal inflammation, the infiltration of leukocytes into the mucosal layer triggers a substantial elevation in FL content. Significantly, this protein exhibits insensitivity to proteolytic degradation and retains its stability in fecal samples, even when leukocyte morphology is damaged by transportation, storage, swab processing, or exposure to toxins[75], suggesting that FL may serve as a potentialbiomarker for IBD diagnosis or disease activity monitoring.

Calprotectin is a 36-kDa calcium-binding protein belonging to the S100 protein family[76]. It is primarily synthesized and released by neutrophils, where it constitutes approximately 60% of the total cytosolic protein content[77]. In addition to its direct antimicrobial effects, calprotectin contributes to the innate immune response by serving as an endogenous damage-associated molecular pattern (DAMP) molecule that activates TLR4. Calprotectin is present in multiple body fluids, with its concentrations corresponding to the degree of existing inflammation; FC levels are approximately six times higher than those observed in plasma[77]. FC is closely correlated with the clinical, endoscopic, and histological manifestations of disease activity in UC, making it useful for monitoring clinically stable patients[78], although thresholds and the criteria for diagnosing endoscopic remission or healing remain inconsistent across research investigations. It is generally accepted that levels <100 μg/g signify a high likelihood of endoscopic remission, values of 100-200 μg/g denote an intermediate probability, and values exceeding 200 μg/g indicate a low probability of achieving endoscopic remission[72].

The findings revealed that the FL trajectory exhibited the highest area under the curve (AUC) values for forecasting endoscopic, histological, and clinical remission, outperforming all other single biomarkers (FL, CRP) and their respective trajectories in this prognostic assessment[79]. A positive correlation of FL and CRP with disease activity index was identified in another study[80], while no corresponding correlation was detected for white blood cells. FL was shown to be able to distinguish

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between mild versus moderate, and mild versus severe disease activity in the UC patient cohort. A prospective study demonstrated that FC exhibited significantly higher sensitivity and specificity for relapse prediction than FL or hemoglobin. Additionally, fecal biomarkers showed a significant positive correlation with Mayo endoscopic subscore (MES). Notably, FL and FC outperformed MES in predictive performance, as MES has limited objectivity in distinguishing between grades 0 and 1[81].

4.2. Intestinal Ultrasound in Monitoring Remission in UC

Intestinal ultrasound (IUS) offers a non-invasive, low-cost, radiation-free, and repeatable option that requires minimal bowel preparation and is more acceptable to patients[82]. UC has long been considered an IBD confined to the mucosal layer. Recent findings, however, provide new evidence for challenging this traditional dogma, indicating that UC is not restricted to the intestinal mucosa and may involve deeper intestinal tissues. IUS-based real-time in vivo imaging has detected multiple transmural lesions in UC, such as increased bowel wall thickness (BWT), loss of haustrations and wall stratification, and mesenteric fibrofatty proliferation, among which BWT is the most frequently adopted parameter of IUS for assessing disease activity and has been shown to have the closest association with endoscopic disease activity in the colon. IUS shows persistent and prominent submucosal changes even during endoscopic remission[83]. In a retrospective cohort of 51 moderate-to-severe UC patients, BWT showed a highly significant positive correlation with both serum CRP levels ($p = 0.0001$) and the MES ($p < 0.0001$)[84]. IUS has shown a sensitivity of 95% and a specificity of 96% in detecting UC[85]. By utilizing IUS, clinicians can identify early warning signs of disease recurrence, such as BWT, and initiate timely interventions to prevent further disease progression. However, IUS exhibits a sensitivity of merely 15% when evaluating disease progression and complications in the rectum due to the rectum's deep anatomical position in the pelvis. This may limit the modality's effectiveness in the treatment monitoring of active UC[85].

4.3. Diffusion-Weighted Imaging and Intravoxel Incoherent Motion in Monitoring Remission in UC

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique that assesses the diffusion of water molecules in biological tissues. It generates image contrast based on variations in water diffusion across different tissue microenvironments. Therefore, DWI provides meaningful information about the cellular structure and tissue organization at the microlevel. DWI assesses intestinal mucosal barrier integrity indirectly by detecting alterations in water molecule diffusion, rather than directly visualizing the barrier structure itself. A normal barrier shows high apparent diffusion coefficient (ADC) values due to free water diffusion. During active UC, inflammation (mucosal congestion, edema, inflammatory cell infiltration, and epithelial cell apoptosis) increases cellular density and restricts water diffusion, resulting in high DWI signal and low ADC values. This makes DWI valuable for diagnosing, assessing disease activity, and monitoring treatment response of UC[86,87].

A cohort of 20 individuals with UC showed that the MR-score was highly correlated with the endoscopic modified Baron score. Quantitative analysis of ADC values was conducted concurrently, and the ADC values of bowel segments confirmed inflamed by endoscopy were markedly lower than those of normal segments. DWI provides a quantitative approach for distinguishing actively inflamed intestinal segments from normal mucosa, thereby enabling the accurate detection of UC. However, quantitative DWI assessment has limitations: the reproducibility and reliability of ADC mapping are compromised by the lack of standardized acquisition protocols and inconsistent post-processing methods. Furthermore, ADC measurements exhibit significant variability across different scanner platforms[86,88].

DWI eliminates the requirement for oral and rectal bowel preparations, fasting, and intravenous contrast administration[89]. Furthermore, its relatively short scan acquisition time renders DWI particularly suitable for paediatric patients[90]. As DWI requires no contrast agents, it effectively circumvents complications linked to gadolinium-based contrast media, including allergic reactions,

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renal dysfunction[91], and the risk of prolonged gadolinium retention in the central nervous system[92]. Notably, bowel preparation is associated with acute disease exacerbation in patients with UC, and thus the use of DWI has the potential to reduce the risk of triggering such acute complications in this patient population[93].

Intravoxel incoherent motion (IVIM) is a functional MRI technique based on DWI, and it breaks through the limitations of conventional DWI, which conflates diffusion and perfusion signals, thus providing more comprehensive insights into tissue microenvironment. IVIM is proving especially useful in pathologies with notable tissue hyperperfusion, i.e. neoplastic or inflammatory conditions[94]. The fundamental mechanism of IVIM relies on a bi-exponential signal attenuation model. This model accounts for the reduction in MRI signal intensity corresponding to different b-values and includes three key parameters: 1. True diffusion coefficient (D), which reflects the degree of water molecule restriction in the tissue. A lower D value typically indicates increased cellularity or tissue edema, which is common in inflammatory lesions. 2. Pseudo-diffusion coefficient (D*), which is positively correlated with microcirculatory perfusion level. 3. Perfusion fraction (f), which refers to the proportion of the microcirculatory perfusion in the total signal. Inflammation induces an increase in microcirculatory perfusion[89]. The efficacy of IVIM in evaluating inflammatory activity of UC has been explored in a study. IVIM-derived parameters and histopathological data were compared across 34 intestinal segments in UC patients, with marked differences identified between moderate to severe inflammation (grades 3-5) compared with less-active or non-active disease (grades 0-2) (Parameters f and D showed significant differences, but no significant difference was found in D*)[95]. This study confirms that IVIM parameters exhibit notable variations corresponding to different histological inflammatory grades in UC. The results are encouraging yet require further validation in larger, multicenter studies.

A comparison of several common non-invasive monitoring methods in terms of sensitivity, specificity, reproducibility, cost and clinical applicability is shown in Table 1.

Table 1. Comparison of common non-invasive monitoring methods for ulcerative colitis.

Modality	Technical Principle	Clinical Application	Strength	Limitation
Fecal Biomarkers	Fecal calprotectin (FC) and fecal lactoferrin (FL) testing	1. Monitor disease activity in clinically stable UC patients[80]; 2. Predicting endoscopic, histological, and clinical remission[81]; 3. Distinguish disease activity[82]; 4. Serving as useful markers for IBD[77].	1. Completely non-invasive, easily obtainable samples; 2. FL has strong stability, resistant to proteolytic degradation[77]; 3. FC/FL highly correlate with clinical, endoscopic, and histological findings[80]; 4. FL and FC outperformed MES in predictive performance[83].	1. Inconsistent FC thresholds for endoscopic remission across studies[74]; 2. Cannot localize inflammation site, does not display structural lesions.
Intestinal Ultrasound (IUS)	Real-time ultrasound to directly visualize the macro-structure of the intestinal wall[62,63].	1. Assessing UC disease activity[85,86]; 2. Monitoring remission period[85,86],and identifying early warning signals for timely intervention to prevent disease progression[88]; 3. Detecting transmural lesions[85,86].	1.Non-invasive, radiation-free, low-cost, minimal bowel preparation required and highly acceptable [84]; 2. Can display transmural lesion and bowel wall thickness; 3. BWT significantly correlates with CRP and MES[87]; 4.Sensitivity of 95% and specificity of 96% for the diagnosis of colonic lesions[88].	1. Low sensitivity for the evaluation of rectal lesions[88]; 2. Limited evaluation of deep and complex complications.
Diffusion-Weighted Imaging (DWI)	MRI technology based on water molecule diffusion motion, with quantitative analysis via ADC values	1.UC diagnosis, inflammatory activity assessment, grading and treatment response monitoring[89,90]; 2.Differentiation of active inflammatory lesions from normal mucosa; 3.Suitable for children, patients intolerant to bowel preparation or with contrast allergy[93–95].	1.Radiation-free, with no contrast agent, bowel preparation, or fasting required[92]; 2. Avoids gadolinium-related complications[94,95]; 3. Fast scanning, suitable for children[93].	1. Large variation in results across different equipment; no standardized protocol for ADC values, affecting reproducibility and reliability of ADC maps[89,91]; 2. Only indirectly reflects mucosal barrier.
Intravoxel Incoherent Motion (IVIM)	DWI-based advanced MRI using a bi-exponential model to obtain D, D* and f	1. Assessing UC inflammation and grading disease activity[98]; 2. Particularly useful in pathological states with significant tissue hyperperfusion[97].	1. Separates diffusion and perfusion signals, more comprehensively reflects tissue microenvironment[97]; 2. Provides more comprehensive tissue microenvironment information[97].	1. Still in the research stage and requires multi-center validation; 2. Technically complex with low clinical availability.

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5. New Therapeutic Strategies Targeting the Epithelial Barrier

Conventional therapeutic approaches for UC predominantly target downstream inflammatory responses. In contrast, this section focuses on strategies that directly target the epithelial barrier, such as regulating tight junction proteins, promoting epithelial cell regeneration, upregulating MUC2 expression, and modulating the microbiota and their metabolites. These approaches hold great promise for developing more curative therapies for UC.

5.1. Targeting Tight Junctions

5.1.1. Zonulin Pathway Inhibition

Larazotide, a synthetic octapeptide, functions as a competitive inhibitor of the apical zonulin receptor, thereby counteracting zonulin-mediated intestinal permeability by preventing the disassembly and opening of tight junctions. This agent was the first molecule described to serve as a tight junction regulator through the restoration of hyperpermeable junctions to their closed physiological state[96].

In murine models, short-term administration of the zonulin antagonist larazotide alleviated intestinal inflammation, reversed colon shortening, and enhanced barrier integrity, while also reducing arthritis onset[37]. Furthermore, in IL-10-deficient (IL-10$^{-/-}$) mice, which spontaneously develop colitis with increased small intestinal permeability preceding clinical symptoms, larazotide treatment significantly decreased permeability and attenuated disease markers[97]. Additionally, rectal administration of larazotide in a DSS-induced UC mouse model ameliorated weight loss, lowered disease activity index scores, reduced serum FITC-dextran levels, and upregulated tight junction proteins (ZO-1, occludin, claudin-5). These findings demonstrate that larazotide restores epithelial integrity by enhancing tight junction protein expression, offering a promising therapeutic strategy for IBD-associated barrier dysfunction[98].

5.1.2. JAK-STAT and MLCK Pathway Inhibition

Tofacitinib, the first approved JAK inhibitor for moderate-to-severe UC treatment, is a small-molecule JAK inhibitor that targets JAK1 and JAK3. It compromises intracellular signaling in specific immune cells by blocking signal transducer and activator of transcription (STAT) protein phosphorylation and subsequent dimerization, leading to diminished inflammatory cytokine production[99]. Unlike biologic agents (e.g., TNFα inhibitors), tofacitinib is not susceptible to anti-drug antibodies, offering a notable clinical advantage[100]. Treatment with Tofacitinib not only effectively reduced the inflammatory parameters, but also decreased the expressions of pore-forming proteins claudin-2 and claudin-15, and improved the loss of colonic mucosal integrity in colitis rats induced by TNBS. Demonstrated that tofacitinib may restore colonic barrier function under inflammatory conditions[101].

MLCK serves as a key signaling node regulating epithelial tight junctions. Its activation induces MLC phosphorylation, disrupting tight junctions and increasing paracellular permeability, thereby compromising intestinal barrier function[102]. The small molecule Divertin restores barrier function after TNF-induced injury and prevents disease progression in experimental chronic IBD by blocking MLCK1 recruitment to the PAMR without inhibiting its enzymatic activity, thus avoiding toxicities associated with direct MLCK inhibition[103]. Similarly, epicatechin, a natural product derivative, binds MLCK1 and disrupts its interaction with the chaperone FKBP8, preventing pathological MLCK1 recruitment while preserving basal enzymatic activity. Epicatechin effectively alleviates severe immune checkpoint inhibitor-induced colitis by preserving barrier integrity and preventing aberrant immune cell infiltration. Unlike conventional anti-inflammatory agents or immunosuppressants, epicatechin does not inhibit canonical inflammatory pathways such as NF-κB; instead, it functions as a physical barrier stabilizer by specifically blocking aberrant MLCK1

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recruitment[104]. This mechanism offers a novel strategy for mitigating immune-related adverse events: repairing intestinal barrier function through selective disruption of the MLCK1-FKBP8 interaction rather than systemic immunosuppression.

5.1.3. Targeted Delivery of Tight Junction Regulators

Fengnan Yu et al.[98] developed a dual-crosslinked mucus-mimetic hydrogel (HSMP-LA) composed of hyaluronic acid (HA) loaded with ε-polylysine (ε-PL) and larazotide (LA). HA provided biocompatibility, mucoadhesion, and hydration capacity to support mucosal healing[105]. The antimicrobial properties of ε-PL enabled targeting of Gram-positive bacteria, Gram-negative bacteria, and fungi. Additionally, the cationic nature of ε-PL enhanced adhesion of the HSMP hydrogel to the intestinal mucosa. LA functioned as a zonulin receptor antagonist to actively restore tight junctions and epithelial integrity[106]. This complex offers three key advantages: strong adhesion to inflamed tissues with resistance to peristaltic clearance, creation of an antimicrobial microenvironment conducive to mucosal healing, and enhanced restoration of tight junctions through sustained LA release. Following rectal administration in a colitis mouse model, HSMP-LA competitively blocked zonulin-MLCK/p-MLC signaling and upregulated tight junction protein expression, thereby restoring epithelial barrier integrity.

5.2. Targeting Intestinal Epithelial Cell

5.2.1. Autophagy-Apoptosis Balance Modulation

Dapagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor and a classic agent for type 2 diabetes mellitus, has been shown to activate the AMPK/mTOR pathway, thereby enhancing colonic autophagic flux in rats with 2,4,6-Trinitrobenzenesulfonic acid (TNBS)-induced colitis. It also inhibits apoptosis by decreasing caspase-3 activity and cleavage, as well as lowering the Bax/Bcl-2 ratio. Furthermore, dapagliflozin alleviates inflammatory responses and oxidative stress, which synergistically maintain the autophagy-apoptosis balance and protect against colonic mucosal injury. These results demonstrate that dapagliflozin exerts a protective effect against intestinal barrier disruption in colitis by regulating the autophagy–apoptosis balance[107]. Based on this rationale, the SGLT2 inhibitor dapagliflozin is currently being investigated for its effects on intestinal epithelial cell autophagy, apoptosis, and barrier function in patients with IBD (Phase 2 /Phase 3, NCT05986136).

5.2.2. Targeted Delivery for Epithelial Regeneration

Rabex is a plant-derived extracellular vesicle isolated from purple cabbage. Oral administration of Rabex significantly ameliorates the disease activity index, alleviates colon shortening, and reduces histopathological damage (such as inflammatory cell infiltration and goblet cell depletion) in mice with DSS-induced colitis. Its mechanisms are associated with inhibiting the expression of pro-inflammatory factors including TNF-α and IL-1β, promoting the regeneration and repair of colonic epithelial cells, and suppressing DSS-induced cell death. Targeted vesicles (t-Rabex) were prepared by covalently conjugating hyaluronic acid onto their surface, thereby exhibiting enhanced gastrointestinal targeting. The uptake efficiency of t-Rabex in colonic epithelial cells and macrophages was significantly higher than that of unmodified Rabex, and its therapeutic efficacy was comparable to that of Rabex administered at a tenfold higher dose[108].

5.3. Targeting MUC2

5.3.1. Natural Products and Herbal Medicines

Many herbs exhibit protective effects on the mucus barrier. For instance, an infusion of *Copaifera malmei* Harms leaves ameliorates experimentally induced colitis by increasing goblet cell counts,

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promoting mucus secretion, and thereby reinforcing mucus layer integrity[109]. In addition, by targeting key proteins in the necroptosis pathway, hesperidin prevents the death of intestinal epithelial cells (including GCs), elevates colonic MUC2 expression, and contributes to the restoration of the mucus barrier in DSS-induced colitis[110].

5.3.2. Nanoparticles

Nanocrystalline cellulose (NCC), derived from plant fibers, exhibits excellent biocompatibility and high biosafety. Unlike conventional medications, it does not cause systemic toxicity. NCC up-regulates the expression of MUC2, ZO-1, and occludin, thereby restoring the intestinal chemical and mechanical barriers. It also modulates the gut microbiota to restore the biological barrier. Thus, NCC may be a practical therapeutic alternative for UC[111]. Chrysin is a flavonoid with anti-inflammatory and antioxidant effects, but its oral bioavailability is limited. To overcome this drawback, chrysin was loaded into colon-targeted nanoparticles (P@CMPs) for IBD treatment. These nanoparticles bypass the harsh gastrointestinal environment and selectively accumulate in inflamed colonic tissues. In a DSS-induced colitis mouse model, orally administered P@CMPs showed prolonged intestinal retention, strong reactive oxygen species (ROS)-scavenging activity, and reduced pro-inflammatory cytokine levels, thereby upregulating MUC2 expression and promoting mucosal homeostasis. Notably, P@CMPs restored MUC2 expression more effectively than free chrysin. Overall, this colon-targeted delivery strategy alleviates colonic inflammation and protects the intestinal mucus barrier[112].

5.4. Modulation of Microbiota and Metabolites

The gut microbiota is a core regulator of intestinal homeostasis. Dysbiosis of gut microbiota may disrupt the intestinal epithelial barrier, trigger inflammatory cytokine infiltration, and thus contribute to the development of gut-related disorders[113].

5.4.1. Butyrate-Producing Bacteria and SCFA Strategies

Clostridium butyricum, a butyrate-producing bacterium, has been reported to effectively prevent colitis in mice, through reducing serum pro-inflammatory cytokines and enhancing the expression of intestinal barrier proteins, including claudin-3, occludin, ZO-1, and ZO-2, thereby reinforcing intestinal integrity[114]. The administration of *Clostridium butyricum* MIYAIRI 588 (CBM 588) showed a protective effect on intestinal barrier by upregulating the expression of MUC-2 and ZO-1 proteins[115]. *Lactobacillus plantarum*, a versatile lactic acid bacterium derived from multiple sources, has great preventive and therapeutic effects on UC and restores the intestinal barrier. Multiple mechanisms underlie the beneficial effects of *Lactobacillus plantarum* on intestinal barrier function in UC. These include elevating SCFA production, modulating the immune response, attenuating oxidative stress, upregulating tight junction protein expression, accelerating mucin biosynthesis, and reshaping the gut microbiota[116]. MH002, a live biotherapeutic product (LBP) composed of six well-defined bacterial strains belonging to the core human gut microbiome, has been associated with mucosal barrier protection and immunomodulatory functions[117]. This bacterial consortium was formulated to elevate intestinal butyrate concentrations and thereby exert local beneficial effects on gut health. MH002 is currently being evaluated in a phase 2 randomized, double-blind, placebo-controlled trial to assess its efficacy in patients with mild-to-moderate UC (NCT07296915).

5.4.2. Dietary Intervention

The ketogenic diet (KD) is a nutritional intervention distinguished by its high-fat and low-carbohydrate composition. Originally developed as a therapeutic regimen for drug-resistant epilepsy, it has recently attracted growing attention as a potential strategy to alleviate intestinal inflammation[118]. The therapeutic promise of KD is closely linked to its regulatory effects on gut microbiota and related metabolic profiles, although it was also noted that KD implementation may

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result in reduced bacterial diversity[119]. In a murine UC model, KD altered the gut microbiome composition by enriching beneficial bacteria such as *Akkermansia* and *Roseburia*, as well as their metabolites. This shift reduced the production of colonic group 3 innate lymphoid cells (ILC3s) and pro-inflammatory cytokines, while increasing the expression of tight junction proteins (Occludin, ZO-1), MUC-2, and goblet cell numbers[118].

A case series demonstrated promising effects of a ketogenic diet in 10 IBD patients. All patients reported significant, sustained improvements in quality-of-life scores (IBDQ-32), with some successfully stopping medication. The report also emphasizes the need for prospective controlled trials due to limitations like selection bias[120].

Collectively, dietary interventions like the ketogenic diet may restore intestinal barrier function by precisely modulating the gut microbiome—selectively enriching beneficial bacteria (e.g., *Akkermansia, Roseburia*) and their metabolites, while reducing harmful species. This remodeling of microbial metabolism subsequently regulates immune cell populations (e.g., reducing ILC3s) and enhances barrier integrity, positioning microbial metabolism as an upstream regulator of epithelial repair. This represents a targeted, "edit-the-microbiome" strategy for IBD therapy.

6. Conclusions

In summary, the integrity of the intestinal mucosal barrier is central to intestinal homeostasis, and its disruption is a key pathogenic driver in UC. A compromised barrier exposes host tissues to luminal antigens and pathogens, continuously challenging peripheral immune tolerance. This persistent antigenic stimulation triggers aberrant immune activation, establishing a vicious cycle of inflammation and further barrier damage that propels UC initiation and progression[26].

Accurate monitoring is the cornerstone of the treat-to-target strategy, a key principle in modern UC management[72]. Supported by international consensuses such as the STRIDE series, this strategy closely combines the monitoring methods and therapeutic measures. The commonly used clinical monitoring methods have their own advantages and disadvantages: endoscopy combined with pathological biopsy can directly observe the morphology, degree and scope of intestinal mucosal lesions, and is the "gold standard" for diagnosis and monitoring[121], but it is an invasive operation with low patient acceptance; fecal marker detection can indirectly reflect the degree of intestinal mucosal damage; it rapidly indicates the extent of barrier impairment and inflammatory activity, exhibits a strong correlation with disease activity, and holds promise as an important supplement to non-invasive monitoring, yet its specificity remains insufficient. IUS represents a non-invasive, readily available, and cost-efficient alternative for colon visualization as well as the assessment of disease activity, lesion extent, and treatment efficacy, with no requirement for prior bowel preparation. These distinctive advantages render it an optimal modality for point-of-care disease activity monitoring[85,122]. DWI demonstrates high sensitivity in detecting acute inflammation, along with the advantages of a relatively short scan time and good repeatability, which facilitates the dynamic monitoring of lesions. However, it is susceptible to artifacts—such as those from patient motion or magnetic susceptibility—that can compromise image interpretation[87]. Furthermore, the diffusion signal is non-specific, and the technique is not suitable for patients with metallic implants. Barrier function assessment is currently transitioning from static, single-dimensional detection to dynamic, multi-dimensional integration. Future directions lie in constructing a "Digital Twin" model[123] that enables personalized, real-time evaluation of barrier function by integrating three core data layers: multi-omics data layer (who is present), functional sensor layer (how leaky the barrier is), and host immune status layer (T-cell receptor repertoire)[124].

Despite an expanding therapeutic arsenal, achieving deep and sustained remission in UC remains challenging, with induction trials rarely exceeding 20-30% remission rates[2]. This underscores the need for a paradigm shift. While conventional approaches rely on broad-spectrum anti-inflammatories or empirical microbiota modulation (e.g., FMT), frontier research is pivoting towards precision interventions that target root pathophysiological mechanisms. Targeting the epithelial barrier represents one of the promising frontiers in UC therapeutics, positioning tight

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junction proteins, mucus layer integrity, and epithelial regeneration as viable therapeutic targets. However, several challenges remain: the heterogeneity of barrier defects across UC subtypes demands personalized therapeutic matching; and the long-term safety of chronic barrier modulation requires systematic evaluation in large-scale clinical trials. Microbiota-directed therapies have transitioned from empirical probiotics/FMT to targeted microbiota engineering. There is growing recognition that specific bacterial consortia—such as *Akkermansia muciniphila* and butyrate-producing *Roseburia* pecies—are keystone taxa, which supports the development of precise microecological editing based on metabolic regulation. Advanced drug delivery systems constitute a critical enabling technology that enhances the therapeutic index of existing and emerging agents. These systems overcome the fundamental pharmacokinetic limitations of oral biologics and small molecules, including premature gastric degradation, systemic off-target effects, and suboptimal mucosal bioavailability. Future innovations will likely integrate multi-modal responsiveness, combining pH-sensitive release with ROS- triggered activation and mucoadhesive retention to achieve spatiotemporal precision in drug delivery.

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Abbreviations

The following abbreviations are used in this manuscript:

UC	Ulcerative colitis
IBD	Inflammatory bowel disease
sIgA	Secretory IgA
GALT	Gut-associated lymphoid tissue
ALNs	Aggregated lymphoid nodules
IELs	Intraepithelial lymphocytes
LPLs	Lamina propria lymphocytes
GWAS	Genome-wide association studies
ZO-1	Zonula Occludens-1
TNF-α	Tumor necrosis factor α
IFN-γ	Interferon γ
MLCK	Myosin light-chain kinase
MLC	Myosin II regulatory light chain
Zot	Zonula occludens toxin
PKC	Protein kinase C
EGFR	Epidermal growth factor receptor
PAR2	Protease-activated receptor 2
SCFAs	Short-chain fatty acids
SBAs	Secondary bile acids
IECs	Intestinal epithelial cells
5-HT	Serotonin
IPA	Indole-3-propionic acid

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IAA	Indoleacetic Acid
AhR	Aryl hydrocarbon receptor
PXR	Pregnane X receptor
TLR4	Toll-like receptor 4
DCA	Deoxycholic acid
LCA	Lithocholic acid
DSS	Dextran sodium sulfate
AP2M1	Adaptor related protein complex 2 subunit Mu 1
LC3	Protein 1 light chain 3
ATG7	Autophagy related 7
PEAK1	Pseudopodium-enriched atypical kinase 1
HFD	High-fat diet
ER	Endoplasmic reticulum
OXPHOS	Oxidative Phosphorylation
FUT8	Fucosyltransferase 8
FC	Fecal calprotectin
FL	Fecal lactoferrin
PMNs	Polymorphonuclear neutrophils
DAMP	Damage-associated molecular pattern
AUC	Area under the curve
MES	Mayo endoscopic score
IUS	Intestinal ultrasound
BWT	Bowel wall thickness
DWI	Diffusion-weighted imaging
MRI	Magnetic resonance imaging
ADC	Apparent diffusion coefficient
IVIM	Intravoxel Incoherent Motion
STAT	Signal Transducer and Activator of Transcription
HA	Hyaluronic acid
ε-PL	ε-polylysine
LA	Larazotide
TNBS	2,4,6-Trinitrobenzenesulfonic acid
NCC	Nanocrystalline cellulose
ROS	Reactive oxygen species
CBM 588	*Clostridium butyricum* MIYAIRI 588
LBP	Live biotherapeutic product
KD	Ketogenic diet
ILC3s	Group 3 innate lymphoid cells
FMT	Fecal microbiota transplantation

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