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Review

Intestinal Barrier Dysfunction in Ulcerative Colitis: Mechanisms and Therapeutic Perspectives

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Abstract: Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease characterized by persistent mucosal inflammation of the colon and rectum. Although the exact etiology of UC remains incompletely understood, accumulating evidence suggests that intestinal barrier dysfunction plays a central role in disease initiation, progression, and recurrence. The intestinal barrier is a complex system composed of the epithelial layer, tight junction proteins, mucus layer, immune components, and gut microbiota, which together maintain mucosal homeostasis and protect against luminal pathogens and antigens. In UC, impairment of epithelial integrity, altered tight junctions, goblet cell depletion, mucus layer defects, microbial dysbiosis, and exaggerated immune activation contribute to increased intestinal permeability and sustained inflammation. Recent studies have highlighted multiple mechanisms underlying barrier dysfunction in UC, including inflammatory cytokine-mediated signaling, oxidative stress, mitochondrial injury, and dysregulated cell death pathways. Moreover, restoration of barrier integrity has emerged as an important therapeutic goal. Conventional anti-inflammatory agents, biologics, small-molecule compounds, microbiota-based therapies, and several emerging approaches may exert beneficial effects at least partly through improving barrier function. In this review, we summarize the structural and functional components of the intestinal barrier, discuss the major mechanisms of barrier dysfunction in UC, and highlight current and potential therapeutic strategies targeting barrier restoration. A better understanding of intestinal barrier impairment may provide new insights into the pathogenesis of UC and facilitate the development of more effective and personalized treatment approaches.

Keywords: ulcerative colitis; intestinal barrier; epithelial barrier; tight junction; gut microbiota; mucosal inflammation; barrier dysfunction; therapeutic strategies

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1. Introduction

Ulcerative colitis (UC) is a chronic, relapsing, and remitting inflammatory bowel disease that primarily affects the colonic mucosa [1]. The incidence and prevalence of UC have increased worldwide over the past decades, imposing a substantial burden on healthcare systems and patients' quality of life. Clinically, UC is characterized by abdominal pain, diarrhea, rectal bleeding, urgency, and, in severe cases, systemic complications. Despite considerable progress in therapeutic strategies, many patients still experience recurrent disease activity, incomplete mucosal healing, and poor long-term outcomes [2].

The pathogenesis of UC is complex and involves a dynamic interplay among genetic susceptibility, environmental factors, immune dysregulation, and alterations in the gut microbiota. In recent years, growing attention has been paid to the intestinal barrier, which serves as the first line of defense between the luminal environment and the host immune system. Under physiological conditions, the intestinal barrier maintains selective

permeability, allowing nutrient absorption while preventing the translocation of pathogens, toxins, and excessive antigens. Once barrier integrity is compromised, luminal contents can penetrate the mucosa and trigger exaggerated immune and inflammatory responses, thereby contributing to disease onset and perpetuation.

The intestinal barrier is not a single structure but an integrated system composed of the epithelial layer, intercellular junctional complexes, mucus layer, mucosal immune network, and commensal microbiota [3,4]. Increasing evidence suggests that dysfunction of these components is closely associated with UC progression. Disruption of tight junctions, depletion of goblet cells, mucus layer defects, microbial dysbiosis, and inflammatory cytokine overproduction may form a vicious cycle that aggravates mucosal injury. Therefore, a comprehensive understanding of intestinal barrier dysfunction may provide important insights into the pathophysiology of UC and reveal novel therapeutic opportunities. In this review, we summarize the major components of the intestinal barrier, discuss the molecular and cellular mechanisms involved in its dysfunction in UC, and highlight current and emerging therapeutic strategies targeting barrier restoration.

2. Overview of the Intestinal Barrier

The intestinal barrier is a highly organized and dynamic system that separates the luminal environment from the internal milieu while allowing selective absorption of nutrients, water, and electrolytes [5]. It plays an essential role in maintaining intestinal homeostasis by preventing the translocation of pathogenic microorganisms, toxins, and excessive antigens. Rather than being a single anatomical structure, the intestinal barrier consists of multiple interconnected components, including the mechanical barrier, chemical barrier, immune barrier, and microbial barrier. These layers cooperate to preserve mucosal integrity and regulate host–microbe interactions [6].

2.1. Mechanical Barrier

The mechanical barrier is primarily formed by a monolayer of intestinal epithelial cells (IECs), which lines the intestinal mucosa and serves as the first physical obstacle against luminal contents. IECs include absorptive enterocytes, goblet cells, enteroendocrine cells, Paneth-like cells, and stem/progenitor cells located in the crypts. In the colon, epithelial renewal is particularly important because the mucosa is constantly exposed to dense microbial communities and inflammatory stimuli. Continuous epithelial turnover and rapid repair after injury are therefore essential for barrier maintenance [7].

Intercellular junctional complexes are critical for the integrity of the mechanical barrier. These complexes mainly include tight junctions, adherens junctions, and desmosomes [8]. Tight junctions, located at the apical region of adjacent epithelial cells, regulate paracellular permeability and determine the selective passage of ions and small molecules. Major tight junction-associated proteins include occludin, claudins, and zonula occludens proteins such as ZO-1[8]. Adherens junctions and desmosomes provide structural support and promote cell–cell adhesion, thereby contributing to epithelial cohesion and resistance to mechanical stress. Under physiological conditions, these junctional structures maintain a controlled permeability barrier; when disrupted, luminal antigens and microorganisms can more easily penetrate the mucosa and trigger inflammation.

In addition, epithelial restitution and regeneration are indispensable for maintaining the mechanical barrier. Intestinal stem cells located at the base of crypts continuously replenish damaged epithelial cells, while coordinated processes such as cell migration, proliferation, and differentiation ensure efficient mucosal healing. Any disturbance in epithelial renewal or repair may weaken barrier integrity and predispose the intestine to chronic inflammation.

2.2. Chemical Barrier

The chemical barrier mainly consists of the mucus layer, antimicrobial peptides, and secreted immunological mediators. In the colon, the mucus layer is especially important because it provides a protective interface between luminal microorganisms and the

epithelial surface. This layer is largely produced by goblet cells and is rich in mucins, among which MUC2 is the predominant secreted mucin in the colon. The mucus layer acts as a lubricating and protective matrix that limits direct microbial contact with epithelial cells and helps trap pathogens and harmful substances.

Besides mucus, intestinal epithelial cells secrete various antimicrobial molecules, including defensins, lysozyme, regenerating islet-derived proteins, and other peptides that inhibit microbial overgrowth and contribute to host defense. Although Paneth cells are less prominent in the colon than in the small intestine, antimicrobial peptide production remains an important component of mucosal protection. Secretory immunoglobulin A (sIgA), released into the intestinal lumen, also participates in the chemical barrier by neutralizing microorganisms and preventing their adherence to the epithelial surface.

The chemical barrier not only provides local protection but also supports the spatial segregation between commensal microbes and host tissues. Impairment of mucus production, altered mucin composition, or reduced antimicrobial peptide secretion may increase epithelial exposure to luminal bacteria and facilitate inflammatory responses.

2.3. Immune Barrier

The intestinal immune barrier is composed of innate and adaptive immune elements that collectively preserve mucosal tolerance while enabling rapid responses to invading pathogens [9]. This barrier includes epithelial-derived mediators, resident macrophages, dendritic cells, neutrophils, innate lymphoid cells, T lymphocytes, B lymphocytes, plasma cells, and gut-associated lymphoid tissue. Under normal conditions, the intestinal immune system maintains a delicate balance between immune defense and tolerance to commensal microbiota and dietary antigens.

Innate immune cells are essential for the early detection of microbial signals and tissue injury. Pattern recognition receptors, such as Toll-like receptors and NOD-like receptors, recognize pathogen-associated and damage-associated molecular patterns, thereby initiating downstream inflammatory or protective responses. Adaptive immunity further refines mucosal defense through antigen-specific responses [9]. Regulatory T cells, for example, help suppress excessive inflammation and maintain tolerance, whereas effector T-cell subsets may promote inflammatory cascades when dysregulated.

Cytokines and chemokines are central mediators of the immune barrier [10]. Under physiological conditions, their production is tightly controlled to maintain mucosal homeostasis. However, excessive release of proinflammatory cytokines can impair epithelial function, disrupt intercellular junctions, and amplify tissue injury. Therefore, immune homeostasis is indispensable for preserving intestinal barrier integrity.

2.4. Microbial Barrier

The microbial barrier refers to the protective role of the commensal gut microbiota in maintaining intestinal health. The colon harbors a highly diverse microbial community that contributes to nutrient metabolism, colonization resistance, immune education, and barrier regulation [11]. Commensal microorganisms compete with pathogens for ecological niches and nutrients, thereby limiting the expansion of harmful species. They also produce metabolites that influence epithelial function and mucosal immunity.

Among microbial metabolites, short-chain fatty acids (SCFAs), particularly butyrate, are of special importance. Butyrate serves as a major energy source for colonocytes, promotes epithelial integrity, enhances tight junction assembly, and exerts anti-inflammatory effects [12]. Other microbial-derived molecules, including bile acid metabolites and tryptophan-derived products, also modulate immune responses and barrier function. Thus, the microbiota does not merely coexist with the host but actively shapes the intestinal barrier.

Overall, the intestinal barrier is a multifunctional and integrated defense system. The mechanical, chemical, immune, and microbial barriers are closely interconnected, and dysfunction in one component often affects the others. This interdependence is

particularly relevant in ulcerative colitis, in which barrier impairment is increasingly recognized as a central feature of disease pathogenesis.

3. Intestinal Barrier Dysfunction in Ulcerative Colitis

Increasing evidence indicates that intestinal barrier dysfunction is a hallmark of ulcerative colitis and contributes to both disease initiation and persistence. In UC, multiple barrier components are disrupted simultaneously, including epithelial integrity, junctional architecture, mucus production, microbial composition, and mucosal immune balance. These alterations promote increased intestinal permeability, facilitate the translocation of luminal antigens and bacteria, and perpetuate chronic mucosal inflammation [13].

3.1. Epithelial Injury and Impaired Repair

The intestinal epithelium is continuously exposed to inflammatory mediators, oxidative stress, and microbial stimuli in UC. Persistent inflammation can induce epithelial cell injury, apoptosis, and defective restitution, thereby compromising the integrity of the mucosal surface [14,15]. Histologically, UC is often associated with epithelial erosion, ulceration, crypt distortion, and inflammatory infiltrates, all of which reflect substantial epithelial damage.

Under normal conditions, epithelial renewal and regeneration rapidly restore barrier continuity after injury. However, in UC, regenerative processes may become insufficient or dysregulated. Chronic inflammatory stress can impair the proliferative and differentiation capacity of intestinal stem and progenitor cells, reducing the efficiency of mucosal healing. Delayed epithelial repair exposes the lamina propria to luminal contents for prolonged periods, further enhancing immune activation and tissue damage. Thus, epithelial injury and defective repair establish a self-perpetuating cycle that drives disease chronicity [16].

3.2. Tight Junction Disruption and Increased Intestinal Permeability

One of the most important features of barrier dysfunction in UC is the disruption of intercellular junctions, particularly tight junctions. Tight junction proteins such as occludin, claudins, and ZO-1 are frequently altered in inflamed colonic mucosa, leading to impaired paracellular sealing and increased intestinal permeability. This "leaky" barrier allows bacterial components, toxins, and dietary antigens to penetrate the epithelial layer more readily and activate mucosal immune responses.

Proinflammatory cytokines play a major role in tight junction disruption. Tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), and interleukin-13 (IL-13) have all been implicated in the downregulation or redistribution of tight junction proteins. Cytokine-induced activation of myosin light-chain kinase (MLCK) can promote cytoskeletal contraction and increase paracellular permeability. In addition, inflammatory signaling pathways such as NF-κB, JAK/STAT, and MAPK may further aggravate junctional disorganization. These molecular events contribute directly to the loss of barrier selectivity observed in UC.

3.3. Mucus Layer Defects and Goblet Cell Dysfunction

The colonic mucus layer provides critical protection against direct microbial-epithelial contact, and its alteration is a prominent feature of UC. Patients with UC often exhibit goblet cell depletion, reduced mucin secretion, and abnormalities in mucus composition and organization. In particular, decreased expression or altered structure of MUC2 may weaken mucus barrier properties and reduce the capacity to prevent bacterial encroachment.

Goblet cell dysfunction can result from inflammatory injury, altered epithelial differentiation, and dysregulated cytokine signaling [17]. When the mucus layer becomes thinner or structurally defective, commensal and pathogenic bacteria can more easily approach the epithelial surface, triggering innate immune activation and aggravating

mucosal inflammation. Therefore, impairment of the mucus barrier represents a key step linking epithelial vulnerability to sustained inflammatory responses in UC.

3.4. Dysbiosis and Disruption of the Microbial Barrier

Microbial dysbiosis is commonly observed in UC and is characterized by reduced microbial diversity, depletion of beneficial commensals, and expansion of potentially harmful bacteria. Although the precise microbial signatures may vary across studies, a consistent finding is the loss of bacteria associated with SCFA production, especially butyrate-producing species. Because butyrate is essential for epithelial energy metabolism and barrier support, its reduction may contribute to epithelial fragility and impaired barrier restoration [18].

Dysbiosis may also alter the production of bile acid metabolites, tryptophan derivatives, and other microbial products involved in immune and epithelial regulation. At the same time, disruption of the epithelial and mucus barriers facilitates abnormal microbial contact with host tissues, which in turn promotes further dysbiosis. Thus, microbial imbalance is both a cause and a consequence of barrier dysfunction in UC, reinforcing the chronic inflammatory state.

3.5. Immune Dysregulation Associated with Barrier Damage

Barrier dysfunction in UC is closely associated with excessive mucosal immune activation. Once epithelial integrity is compromised, luminal bacteria and antigens gain greater access to the lamina propria, where they stimulate innate immune cells and trigger cytokine production. Activated macrophages, dendritic cells, neutrophils, and lymphocytes release inflammatory mediators such as TNF-α, IL-6, IL-1β, and IFN-γ, which further impair epithelial survival and barrier structure.

This reciprocal interaction between barrier breakdown and immune dysregulation creates a vicious cycle. On the one hand, barrier damage exposes the mucosa to inflammatory triggers; on the other hand, the resulting immune response exacerbates epithelial injury, junctional disruption, and goblet cell loss. Failure to restore immune tolerance and mucosal homeostasis therefore contributes to persistent disease activity and relapse in UC.

3.6. Oxidative Stress and Barrier Injury

Oxidative stress is another important factor contributing to barrier dysfunction in UC [19,20]. During intestinal inflammation, activated immune cells generate excessive reactive oxygen species (ROS), which can directly damage lipids, proteins, DNA, and mitochondrial function in epithelial cells. Elevated oxidative stress impairs epithelial survival, promotes apoptosis or other forms of cell death, and disrupts intercellular junctions.

Moreover, mitochondrial dysfunction may amplify ROS production and compromise cellular energy metabolism, thereby weakening epithelial repair capacity. Oxidative damage can also influence mucin secretion and immune signaling, further aggravating barrier impairment. Therefore, oxidative stress represents an important mechanistic link between inflammation and structural barrier injury in UC.

Taken together, intestinal barrier dysfunction in UC is a multifaceted process involving epithelial injury, junctional disassembly, mucus depletion, microbial imbalance, immune dysregulation, and oxidative stress. These abnormalities are closely interconnected and collectively sustain chronic inflammation. Understanding these processes is essential for identifying therapeutic strategies aimed at restoring mucosal integrity.

4. Therapeutic Perspectives Targeting Intestinal Barrier Dysfunction

Given the central role of barrier impairment in UC, restoration of intestinal barrier integrity has emerged as an important therapeutic objective. Although most current treatments are primarily designed to suppress inflammation, many of them may also improve barrier function indirectly by reducing epithelial injury, normalizing cytokine

profiles, and facilitating mucosal healing. In addition, several emerging approaches more directly target barrier restoration [21,22].

4.1. Conventional Therapies and Barrier Restoration

Conventional agents used in UC, including 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressants, remain fundamental components of treatment. Their primary benefit lies in the attenuation of mucosal inflammation; however, this anti-inflammatory effect can secondarily promote barrier repair. For example, by reducing local cytokine production and oxidative stress, these agents may help preserve epithelial viability, improve tight junction integrity, and support mucosal healing.

5-ASA has been reported to exert antioxidant and anti-inflammatory effects that may protect epithelial cells and reduce permeability. Corticosteroids, while effective in controlling acute flares, can rapidly suppress inflammatory cascades and thereby reduce ongoing barrier injury [23,24]. Immunosuppressive agents such as azathioprine may also contribute to long-term mucosal stabilization in selected patients. Nevertheless, these therapies are not specifically designed to target barrier structure, and their effects on barrier restoration are often indirect and variable.

4.2. Biologic Therapies

Biologic therapies have significantly advanced the management of moderate-to-severe UC and may improve barrier function by interrupting key inflammatory pathways. Anti-TNF agents such as infliximab and adalimumab can reduce epithelial apoptosis, decrease inflammatory cytokine burden, and promote mucosal healing. Because TNF-α is closely involved in tight junction disruption and epithelial injury, blocking this cytokine may help restore junctional integrity and reduce intestinal permeability.

Other biologics, including vedolizumab and ustekinumab, may also confer barrier-related benefits. Vedolizumab inhibits lymphocyte trafficking to the gut by targeting $\alpha4\beta7$ integrin, thereby reducing mucosal inflammation and allowing epithelial recovery. Ustekinumab, through inhibition of IL-12/23 signaling, modulates immune activation and may indirectly improve epithelial and barrier homeostasis. Although these agents are primarily immunomodulatory, their clinical efficacy is closely linked to improved mucosal integrity and healing [25].

4.3. Small-Molecule Drugs

Small-molecule therapies, particularly Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators, represent an important addition to the therapeutic landscape of UC. JAK inhibitors such as tofacitinib can suppress multiple cytokine signaling pathways involved in epithelial injury and immune amplification. By attenuating cytokine-driven inflammation, they may facilitate restoration of tight junctions and epithelial barrier function.

S1P receptor modulators regulate lymphocyte trafficking and may reduce intestinal immune cell infiltration. Through control of mucosal inflammation, these agents may create a more favorable environment for barrier recovery. Compared with biologics, small molecules offer certain practical advantages, such as oral administration, but their long-term effects on barrier integrity and mucosal healing require further investigation [26].

4.4. Microbiota-Based Therapies

Because the microbial barrier is an essential component of intestinal homeostasis, microbiota-based interventions have attracted considerable interest in UC. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) are intended to restore microbial balance, enhance beneficial metabolite production, and improve host–microbe interactions.

Probiotics may strengthen barrier function by increasing SCFA production, inhibiting pathogenic bacteria, modulating immune responses, and enhancing mucus secretion [27]. Prebiotics serve as substrates for beneficial microbes and may indirectly promote barrier-supportive metabolites such as butyrate. FMT has shown promise in some patients with UC by reshaping the gut microbiota and improving clinical outcomes,

although its efficacy remains inconsistent and depends on factors such as donor selection, treatment protocol, and recipient characteristics. Overall, microbiota-based therapies represent a promising but still evolving strategy for barrier restoration.

4.5. Nutritional and Natural Compound Interventions

Nutritional factors and natural compounds may also influence intestinal barrier function in UC. Short-chain fatty acids, especially butyrate, support colonocyte metabolism, enhance tight junction assembly, and exert anti-inflammatory effects. Vitamin D has been implicated in epithelial integrity, immune regulation, and antimicrobial defense, while zinc is important for epithelial repair and barrier maintenance. Deficiency in these micronutrients may compromise mucosal protection.

Natural compounds such as curcumin and polyphenols have been investigated for their antioxidant and anti-inflammatory properties. These agents may help preserve epithelial structure, reduce oxidative damage, and modulate inflammatory signaling. Although evidence from clinical studies remains variable, nutritional and adjunctive interventions could become useful components of comprehensive barrier-oriented management strategies.

4.6. Emerging Barrier-Targeted Therapies

In addition to established anti-inflammatory approaches, several emerging therapies directly or indirectly target barrier repair. These include agents aimed at enhancing tight junction stability, promoting mucus production, stimulating epithelial regeneration, or modulating epithelial cell death pathways. Stem cell-based therapies and exosome-based approaches have also attracted attention due to their potential roles in tissue repair, immunomodulation, and mucosal healing.

Furthermore, advances in biomaterials, nanomedicine, and targeted drug delivery may facilitate localized therapeutic strategies that improve barrier restoration while minimizing systemic adverse effects. As understanding of barrier biology deepens, more precise interventions may be developed to address specific defects in epithelial integrity, mucus function, microbial balance, or immune regulation.

4.7. Challenges and Future Directions in Barrier-Targeted Therapy

Despite growing interest in barrier restoration, several challenges remain. First, it is not always clear whether barrier dysfunction is a primary driver or a secondary consequence of inflammation in individual patients. Second, reliable clinical biomarkers for assessing barrier integrity are still limited. Third, many barrier-related findings are derived from experimental models, and translation to human disease remains incomplete.

Future studies should aim to identify patient subsets with distinct barrier phenotypes and explore personalized therapeutic approaches. Integration of multi-omics technologies, single-cell analysis, and longitudinal clinical cohorts may improve understanding of barrier dysfunction and treatment response. Ultimately, combining anti-inflammatory therapy with more direct barrier-targeted strategies may represent a promising direction for improving long-term outcomes in UC.

5. Conclusion

In summary, intestinal barrier dysfunction is increasingly recognized as a central event in the pathogenesis and progression of ulcerative colitis. Rather than representing an isolated structural abnormality, barrier impairment in UC involves a complex interplay among epithelial injury, tight junction disruption, mucus layer defects, microbial dysbiosis, immune dysregulation, and oxidative stress. These alterations interact in a self-reinforcing manner, leading to increased intestinal permeability, persistent mucosal inflammation, and recurrent tissue damage.

Current therapies for UC, including conventional anti-inflammatory agents, biologics, and small-molecule drugs, may partly achieve their beneficial effects through improving mucosal integrity and promoting barrier restoration. In addition, microbiota-based interventions, nutritional strategies, and several emerging approaches directly

targeting epithelial repair and barrier homeostasis have shown promising therapeutic potential. However, important questions remain regarding the temporal relationship between barrier dysfunction and inflammation, the identification of reliable biomarkers for barrier assessment, and the translation of mechanistic findings into clinical practice.

A deeper understanding of intestinal barrier biology may provide new insights into disease heterogeneity and therapeutic responsiveness in UC. In the future, integrating anti-inflammatory treatment with more precise barrier-targeted interventions may offer a more effective and personalized strategy for disease control and long-term mucosal healing.

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