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IMMUNOPROTEASOME INHIBITION AS AN EMERGING THERAPEUTIC STRATEGY IN INFLAMMATORY BOWEL DISEASE

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ABSTRACT
Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a chronic, relapsing disorder of the gastrointestinal tract with a rapidly rising global prevalence. Despite significant advances in immunomodulators, biologics, and small-molecule therapies, current treatments remain constrained by limited response rates, secondary loss of efficacy, and adverse effects. Increasing evidence implicates genetic susceptibility, impaired mucosal barrier function, gut microbiota dysbiosis, and immune dysregulation—particularly aberrant nuclear factor kappa B (NF-κB) activation—in driving chronic intestinal inflammation. The proteasome, a key regulator of intracellular protein degradation, directly controls NF-κB signaling and other inflammatory pathways. Recent preclinical studies demonstrate that proteasome inhibition, especially selective targeting of the immunoproteasome, effectively suppresses pro-inflammatory cytokine expression, attenuates colitis severity, and promotes mucosal healing, while offering greater specificity and reduced systemic toxicity compared to conventional inhibitors. However, challenges such as systemic adverse effects, epithelial barrier disruption, and limited clinical validation remain significant barriers to translation. Emerging strategies, including nanoparticle-mediated targeted delivery, subunit-specific inhibitors, and rational combination with existing immunomodulators or biologics, are under active exploration to optimize efficacy and safety. Furthermore, biomarker-guided patient stratification and long-term safety studies are essential to establish therapeutic viability. Collectively, proteasome inhibition represents a promising and mechanistically rational approach to IBD management, with the potential to overcome limitations of existing therapies. Advancing selective, locally targeted, and clinically validated inhibitors could position immunoproteasome modulation as a transformative strategy in refractory IBD treatment.

KEY WORDS
Inflammatory Bowel Disease, Proteasome Inhibition, NF-κB, Immunoproteasome, Targeted Therapy, Intestinal Inflammation

1. INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disorder of the gastrointestinal tract. In recent decades, the epidemiology of IBD has transformed significantly[1]. Globally, the incidence of inflammatory bowel disease reached 8.77 cases per 100,000 in 2021, with prevalence in high-income regions such as Canada exceeding 660 per 100,000, while middle-income countries are experiencing rising incidence due to industrialization and Westernization of lifestyles[2,3]. As a worldwide illness, IBD poses a significant threat to human health and also imposes substantial financial strains on individuals, families, and society.

The precise etiology of IBD remains incompletely understood. However, it is now recognized as a multifactorial disease involving genetic susceptibility, epithelial barrier dysfunction, gut microbiome alterations, dysregulated immune responses, environmental and lifestyle influences[4,5].

Recent advances have expanded therapeutic options for IBD, including pharmacotherapies (aminosalicylates, corticosteroids, immunomodulators, and biologics) as well as surgical management when indicated[6].

The development of targeted inhibitors of tumor necrosis factor (TNF) represents a significant breakthrough, allowing for prolonged remission and altering the course of IBD in a considerable portion of patients[7]. Nonetheless, primary non-response rates to anti-TNF therapy reach up to 40% in clinical trials and 10–20% in real-world series, while secondary loss of response can occur in 23–46% of patients within one year. These limitations underscore the need for novel therapeutic approaches[8].

The proteasome has emerged as a critical regulator of immune and inflammatory processes implicated in IBD pathogenesis. Proteasome inhibitors (e.g., bortezomib) have shown efficacy in preclinical colitis models, primarily through inhibition of dysregulated nuclear factor kappa B (NF-κB) signalling. This pathway is often hyperactivated in IBD, contributing to sustained inflammation and tissue damage.

The immunoproteasome, an inducible proteasome isoform in immune cells, represents a promising target for selective inhibition, potentially reducing inflammation with fewer off-target effects than conventional inhibitors. Recent studies demonstrate that selective immunoproteasome inhibitors attenuate experimental colitis, supporting their further clinical evaluation as innovative IBD therapies[9,10,11].

2. PATHOPHYSIOLOGY OF IBD

IBD arises from a multifactorial interplay of immune dysregulation, genetic susceptibility, epithelial barrier alterations, microbiota imbalance, environmental influences, and molecular signaling abnormalities. These mechanisms collectively drive chronic intestinal inflammation and tissue damage.

2.1 Immune Dysregulation and Inflammatory Response: IBD arises from a dysregulated immune response involving both innate and adaptive immune cells reacting abnormally to intestinal microbiota in genetically predisposed individuals. UC predominantly exhibits a T-helper 2 (Th2)-type immune profile, whereas CD is characterized by a predominance of Th1 and Th17 responses. Dysregulated interactions among neutrophils, macrophages, dendritic cells, innate lymphoid cells, and CD4+ T cell subsets (Th1, Th2, Th17, Th22, Tregs) amplify inflammation. Persistent production of cytokines such as TNF-α, IL-1β, IL-6, and IL-17 sustains mucosal injury[12,13,14,15].

2.2 Genetic and epigenetic Factors: Genomic studies have identified over 240 genetic loci associated with increased susceptibility to IBD, underscoring the strong genetic component of the disease. Key genetic variants influence immune system regulation, epithelial barrier integrity, and microbial interactions. Nevertheless, genetic predisposition alone is insufficient, and complex gene-environment interactions, including epigenetic modifications, are critical in disease onset and progression[13,16]. In addition, epigenetic mechanisms—including DNA methylation and histone modifications—alter immune regulation and epithelial integrity, while aging and metabolic changes

further shape disease susceptibility[17].Rare **monogenic IBD forms** also provide insight into critical immune and barrier pathways[18].

2.3 Epithelial Barrier Dysfunction and Mucosal Damage: Impaired epithelial barrier integrity increases intestinal permeability, allowing luminal antigens and microbes to trigger inflammation. This disruption results from dysregulated apoptosis, altered tight junction proteins, and defective mucus production. Persistent injury leads to impaired ion transport, water retention in the lumen, and diarrhea[19,20,21].

2.4 Microbiota Dysbiosis: Alterations in the gut microbiota composition (dysbiosis) contribute significantly to IBD pathogenesis. There is a depletion of beneficial commensals such as Akkermansia muciniphila and an increase in potential pathobionts like adherent-invasive Escherichia coli (AIEC). These microbial changes affect immune modulation and may induce neurogenic inflammation and pain via the enteric nervous system. Dysbiosis leads to aberrant immune activation and chronic inflammation [12,22,23].

2.5 Environmental and Lifestyle Factors: Environmental factors, including diet, smoking, stress, and early life exposures, modulate IBD risk and progression by influencing gut microbiota and immune responses. Dietary patterns with high pro-inflammatory potential increase disease risk, whereas diets such as the Mediterranean type have protective effects by promoting a healthy microbiome and reducing inflammation. Stressful life events and certain exposures may exacerbate disease activity[24,25].

2.6 Neuro-Immune Interactions: Recent work highlights that inflammation can activate the enteric nervous system, triggering neurogenic inflammation and visceral hypersensitivity, contributing to abdominal pain. Neuropeptides and neurohormones such as neuropeptide Y (NPY) family members are implicated in modulating gut inflammation, influencing disease symptoms and potentially representing therapeutic targets[1,26,27].

2.7 Signaling Pathways and Molecular Mechanisms: Key intracellular signaling cascades, including NF-κB, JAK/STAT, and MAPK pathways (e.g., p38 MAPK), are activated in IBD, facilitating the production of proinflammatory cytokines and chemokines. Targeting these pathways has therapeutic potential, as seen in biologics like anti-TNF agents that reduce inflammation effectively[28,29].

To visually summarize the complex interplay of factors driving inflammatory bowel disease pathogenesis, the Fig. 1 highlights key genetic, environmental, immune, and cellular mechanisms leading to chronic intestinal inflammation and its complications

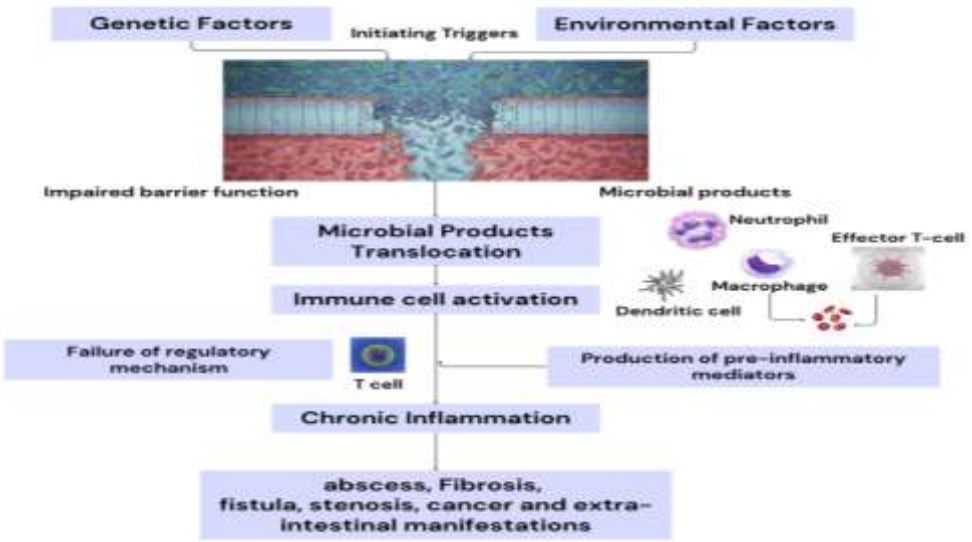

Figure 1: Schematic diagram for the pathogenesis of IBD[30]

3. NF-κB SIGNALLING IN IBD

NF-κB is a master transcription factor critically involved in the pathogenesis of IBD. It regulates immune response, inflammation, apoptosis, and epithelial barrier function, all of which are dysregulated in IBD[31].

3.1 Aberrant Activation and Pathogenesis

Aberrant NF-κB activation in intestinal epithelial cells (IECs) and immune cells is a hallmark of IBD, driving persistent inflammation and mucosal injury. Under resting conditions, NF-κB dimers are sequestered in the cytoplasm by IκB proteins. Upon stimulation with cytokines such as TNF-α and IL-1β, or microbial components like lipopolysaccharide (LPS), the IκB kinase (IKK) complex phosphorylates IκB, leading to its ubiquitination and proteasomal degradation. This allows NF-κB to translocate to the nucleus, where it induces transcription of genes encoding inflammatory mediators, including cytokines, chemokines, and adhesion molecules, thereby sustaining chronic inflammation in IBD[31].

3.2 Genetic and Molecular Regulators

Genetic variants influence NF-κB activity in IBD. For example, mutations in NOD2 alter microbial recognition and signaling through the NOD2–RIPK2–IKK axis, thereby enhancing NF-κB activation. Ubiquitination enzymes, including N4BP3, further regulate this process by modulating RIPK2 ubiquitination, highlighting molecular checkpoints that contribute to excessive inflammation[32].

3.3 Impact on Intestinal Barrier

NF-κB regulates tight junction proteins such as occludin, claudins, and E-cadherin. Dysregulation of this pathway disrupts epithelial barrier integrity, allowing microbial translocation and amplifying mucosal inflammation[33]. Additionally, NF-κB promotes epithelial apoptosis, further compromising barrier function and contributing to ulceration, a hallmark of active IBD[34].

3.4 Cross-talk with Other Pathways

NF-κB signaling interacts with other pathways including MAPK, JAK-STAT, and hypoxia-inducible factor (HIF). These interactions amplify pro-inflammatory cytokine production, reactive oxygen/nitrogen species generation, and T-cell differentiation, thereby shaping disease progression and tissue remodeling.[33,36].

3.5 Therapeutic Implications

Targeting NF-κB is central to IBD therapy:

- **Corticosteroids & Sulfasalazine**: reduce NF-κB activation and pro-inflammatory mediator expression[36].
- **Clarithromycin**: suppresses NF-κB in macrophages and reduces colitis severity[37].
- **Plant sterols (e.g., Guggulsterone)**: inhibit IKK and attenuate colitis[38].
- **Probiotics (Bifidobacterium lactis)**: suppress NF-κB activation in IECs, alleviating colitis[39].

However, complete inhibition of NF-κB may impair epithelial healing, underscoring the need for selective modulation rather than broad suppression[35,40].

NF-κB activation is tightly regulated by the ubiquitin–proteasome system, which controls IκB degradation. Dysregulation of this process contributes to persistent inflammation in IBD, providing a direct mechanistic link between NF-κB signaling and proteasome function[31,32].

4. PROTEASOME STRUCTURE AND FUNCTION

The proteasome is a large multi-subunit protease complex essential for selective degradation of intracellular proteins through the ubiquitin-proteasome system (UPS). This regulated proteolytic activity is critical to maintaining cellular homeostasis by removing damaged, misfolded, or regulatory proteins.

The 26S proteasome, a key form in eukaryotes, consists of a 20S core particle and one or two 19S regulatory particles. The 20S core is a cylindrical structure with four stacked rings, each comprising seven subunits; among them, three β-subunits exhibit proteolytic activity (chymotrypsin-like, trypsin-like, and caspase-like)[41,42]. The 19S regulatory particle recognizes polyubiquitylated substrates, unfolds them, and translocates them into the core for degradation in an ATP-dependent manner[43,44].

Proteasome function is crucial for immune regulation, cell cycle control, and stress responses. Under oxidative stress conditions, proteasome activity can be dynamically regulated, and adaptive responses occur through changes in proteasome composition and interaction with activator complexes like PA28, which enhance degradation of oxidized or damaged proteins[42,45]. Dysfunction or inhibition of proteasome activities can lead to accumulation of damaged proteins, contributing to cellular dysfunction and death[46,47].

5. PROTEASOME AND IBD PATHOPHYSIOLOGY

In the context of inflammatory bowel disease (IBD), proteasome function appears to intersect with disease pathophysiology primarily through immune regulation and inflammation control. IBD is characterized by chronic inflammation of the gastrointestinal tract, where disruption of intestinal epithelial barrier and immune dysregulation play key roles[48,49].

The proteasome modulates key signaling pathways, such as NF-κB, which is activated in response to proinflammatory stimuli and involved in cytokine expression and immune cell activation during IBD[50].

Specifically, proteasome inhibition impacts neutrophil activities by modulating proteins like MCPIP-1, which negatively regulates neutrophil responses including reactive oxygen species (ROS) production and cytokine secretion, suggesting a protective role in IBD inflammation[51]. Additionally, experimental IBD models show that proteasome-mediated protein degradation is integral to maintaining epithelial barrier integrity and immune homeostasis[52]. There is also evidence of cross-talk between oxidative stress and proteasomal function in IBD, whereby proteasome dysfunction exacerbates inflammatory damage through accumulation of oxidatively modified proteins[42].

6. MECHANISM OF PROTEASOME INHIBITION IN IBD

Proteasome inhibition in inflammatory bowel disease (IBD) involves complex mechanisms primarily linked to modulation of immune and inflammatory responses mediated through the ubiquitin-proteasome system (UPS) and NF-kappaB (NF-κB) signaling.

Proteasome inhibitors like MG132 and bortezomib impede the degradation of IκB, preventing NF-κB nuclear translocation and activation. This inhibition reduces the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), diminishing inflammation in IBD models. For example, MG132 reduced TNF-α mRNA, suppressed NF-κB p65 activity, and lowered T cell-mediated immune responses in IL-10-deficient colitis models but might impair mucosal barrier function by affecting epithelial regeneration[53].

Research indicates that TRIM family proteins, known for their E3 ubiquitin ligase activity, are involved in the regulation of the NLRP3 inflammasome, a critical component in mediating intestinal inflammation in. TRIM31 has been shown to enhance the ubiquitin-proteasome pathway's functionality, which may lead to reduced inflammation through NLRP3 modulation and autophagy processes. This reveals a complex interplay between proteasomal function and inflammation, suggesting that disrupting this balance can exacerbate IBD[54,55].

7. IBD MANAGEMENT: TRADITIONAL VS. PROTEASOME APPROACHES

Current therapies for inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, focus on reducing inflammation and maintaining remission. These include conventional treatments such as aminosalicylates, corticosteroids, and immunomodulators (e.g., methotrexate and thiopurines), as well as biologic therapies targeting tumor necrosis factor-alpha (TNF-α), integrins, and interleukins (IL-12/23)[56]. The Figure 1 gives a comparative insight of Current IBD Therapies vs. Proteasome Inhibitors.

Therapy Type	Examples	Mechanism of Action	Efficacy	Limitations/Side Effects
Aminosalicylates	Mesalamine, Sulfasalazine	Anti-inflammatory by inhibiting prostaglandin production	Mild to moderate disease	Hypersensitivity, headache
Corticosteroids	Prednisolone, Budesonide	Suppress immune activation and cytokine production	Effective for induction of remission	Long-term toxicity, adrenal suppression
Immunomodulators	Azathioprine, Methotrexate	Inhibit lymphocyte proliferation	Maintenance therapy	Bone marrow suppression, infections
Biologics	Anti-TNF (Infliximab), Anti-IL-12/23 (Ustekinumab)	Neutralize pro-inflammatory cytokines	High efficacy	Loss of response, infections, immunogenicity
Proteasome Inhibitors	Bortezomib, MG132, Ixazomib	Block proteasomal degradation of IκB, inhibiting NF-κB activation	Preclinical promising efficacy	Potential toxicity, need for selective targeting

Table 1: Comparison of Current IBD Therapies vs. Proteasome Inhibitors[56,57]

Novel agents such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate receptor modulators are emerging to address limitations of existing treatments, including primary and secondary loss of response, side effects, and the need for better safety profiles[56,57].
Proteasome inhibitors offer a promising alternative by directly modulating key inflammatory pathways, notably suppressing NF-κB activation, a central transcription factor in IBD pathogenesis. Unlike some current biologics that target specific cytokines or immune cell trafficking, proteasome inhibitors can broadly inhibit the degradation of IκB, an inhibitor of NF-κB, thus preventing the nuclear translocation and transcription of multiple pro-inflammatory genes[58].

The potential advantages of proteasome inhibitors include:

- **Broad suppression of inflammation:** They modulate several cytokines (e.g., TNF-α, IL-1β, IL-6), providing a multi-targeted anti-inflammatory effect beyond single cytokine blockade[59].
- **Targeting immunoproteasome:** Selective inhibitors of the immunoproteasome, which is upregulated during inflammation, could allow more specific targeting of immune cells involved in IBD with reduced systemic toxicity[59,60].
- **Complementary to existing treatments:** Proteasome inhibitors could be combined with other agents like TNF-blockers or JAK inhibitors to enhance efficacy and reduce required dosages, potentially minimizing side effects[57].
- **Potential for mucosal healing:** By attenuating NF-κB-driven inflammation, proteasome inhibitors might promote mucosal healing, a key treatment goal[56].

However, current clinical use of proteasome inhibitors in IBD is limited, mainly explored in preclinical models demonstrating reduced experimental colitis severity[59]. Clinical trials remain scarce, and concerns about systemic toxicity and off-target effects persist, necessitating development

of selective, locally targeted formulations. Nanoparticle-based delivery systems are under investigation to enhance mucosal targeting, improve efficacy, and reduce systemic side effects[61,62].
Compared to conventional therapies, proteasome inhibitors could offer a more comprehensive immunomodulatory effect with the potential for improved outcomes in refractory cases. Nonetheless, they are not yet standard therapy due to limited clinical evidence and safety concerns relative to biologics and small molecules with established efficacy and tolerability[57,63].
While existing therapies for IBD—ranging from immunomodulators to biologics and small molecules—have improved disease management, proteasome inhibition represents an emerging strategy that may overcome some limitations by broadly suppressing pro-inflammatory signaling pathways. Future research focusing on selective immunoproteasome inhibitors, advanced delivery systems, and combination regimens will clarify their role in complementing or enhancing the current therapeutic landscape for IBD[56-62].

8. PRECLINICAL EVIDENCE OF PROTEASOME INHIBITION IN INFLAMMATORY BOWEL DISEASE

Proteasome inhibitors have been investigated for their potential therapeutic effects in inflammatory bowel disease (IBD), with both preclinical and clinical studies providing insights into their efficacy and mechanisms of action. The following tables contains a list of preclinical and clinical studies of proteasome inhibitors in IBD along with their primary target, main outcomes and adverse effects of that particular inhibitor.

Inhibitor	Primary Target	Model System & Dose/ Regimen	Main Outcomes	Adverse Effects/ Limitations	Reference
MG132	Broad proteasome (β5/β1/β2)	DSS-induced colitis (mice); MG132 used in vivo & IEC culture; dose per study design	Stabilized STAT3, reduced pro-inflammatory cytokines, improved epithelial barrier, ameliorated colitis severity	Non-selective; systemic toxicity at higher doses	64
Bortezomib	Reversible 20S proteasome inhibitor (β5)	DSS colitis (mice); 0.6–1 mg/kg i.p., daily; also TNBS models	Reduced NF-κB activation, decreased TNF-α/IL-6, improved colon histology and weight loss	GI and systemic toxicity at higher doses; mortality in high-dose groups	65
ONX-0914 (PR-957)	Selective immunoproteasome (LMP7/β5i)	DSS colitis (CGRPβ-/- mice); 10 mg/kg s.c. daily ×5 days	↓ DAI, ↓ diarrhoea/bleeding, reduced mucosal inflammation, restored histology	Still preclinical; systemic dosing may cause immunosuppression; long-term safety unknown	66
ONX-0914 (Th17	Selective immunoproteasome (LMP7/β5i)	DSS colitis (mice); ONX-0914	Reduced Th17 frequency, lowered pro-	Limited disease outcome data;	67

modulation)		given during induction	inflammatory cytokines	immune modulation only	
DPLG3	Selective immunoproteasome inhibitor (β5i)	Experimental colitis (mice); systemic dosing	↓ Cytokine production, ↓ immune cell infiltration, improved mucosal protection	Preclinical only; need PK/PD and chronic data	68
YU102	Selective immunoproteasome (LMP2/β1i)	DSS colitis (mice); dosing per study	Attenuated DSS colitis, suppressed NLRP3 inflammasome, improved barrier function	Preclinical stage; need gut-targeted formulations	69

Table 2: Recent preclinical evidence of proteasome inhibitors in inflammatory bowel disease

9. CLINICAL STUDIES SHOWING POTENTIAL OF PROTEASOME INHIBITORS IN IBD

Although no proteasome inhibitor has yet been tested directly in clinical trials for IBD, several related human studies provide important insights into their potential role.

- Bortezomib: A Phase I trial in advanced solid tumors provided insight into dose-limiting toxicities and recommended phase II dose (1.6 mg/m² weekly). Biologic activity included NF-κB pathway inhibition, though diarrhea and hypotension were dose-related adverse events. While not IBD-specific, these data inform safety and dosing[61].
- Sulfasalazine: A common IBD treatment, sulfasalazine inhibits NF-κB activation by blocking IκBα degradation, showcasing indirect proteasome pathway targeting as part of its immunosuppressive mechanism[70].

Clinical application remains limited; further trials are needed to optimize dosing, improve safety, and validate efficacy. Proteasome inhibition remains a promising strategy to modulate NF-κB signaling and other inflammatory pathways in IBD treatment.

10. CHALLENGES AND LIMITATIONS OF PROTEASOME INHIBITION IN INFLAMMATORY BOWEL DISEASE

10.1 Specificity and Off-Target Effects

10.1.1 Broad Inhibition of Cellular Process

Current proteasome inhibitors lack specificity and interfere with diverse cellular processes beyond targeted protein degradation[71]. Given the proteasome's central role in cell cycle progression, immune regulation, and protein homeostasis, non-selective inhibition can trigger toxicities, misfolded protein accumulation, and cellular stress[61]. Off-target effects affecting apoptosis, signal transduction, and cell cycle regulation raise major safety concerns in IBD[71].

10.1.2 Systemic Side Effects

Systemic distribution leads to adverse effects, limiting therapeutic application. Fatigue, gastrointestinal disturbances, and peripheral neuropathy often overlap with IBD symptoms, complicating disease management and drug tolerability[61].

10.1.3. Need for Selective Inhibitors

More selective inhibitors are essential to improve therapeutic index and reduce systemic toxicity Prevention of Experimental Colitis by a Selective Inhibitor of the Immunoproteasome]. Strategies include targeting specific proteasome subunits and tissue-specific delivery to inflamed intestinal sites, enhancing efficacy and safety[59].

10.2. Immunoproteasome Targeting Challenges

10.2.1. Immunoproteasome vs. Constitutive Proteasome

The immunoproteasome, upregulated by inflammatory cytokines, is a relevant IBD target[53]. However, structural overlap with the constitutive proteasome hampers selective inhibition, as non-selective agents disrupt essential cellular functions and cause adverse effects[59].

10.2.2. Subunit-Specific Inhibition

Targeting individual immunoproteasome subunits could improve selectivity, but structural complexity and homology between subunits make selective inhibitor design technically difficult, requiring advanced drug-design approaches[59].

10.2.3. Limited Clinical Data

Clinical evidence on immunoproteasome-specific inhibitors in IBD is scarce. Most studies have assessed general inhibitors, limiting conclusions on their specific benefits. Well-designed clinical trials with appropriate endpoints and biomarkers are needed to establish efficacy and safety[72].

10.3. Intestinal Barrier Disruption

10.3.1. Impact on Epithelial Cell Function

Proteasome inhibition can impair intestinal epithelial cell (IEC) function and barrier integrity, increasing permeability and potentially worsening inflammation. While reducing immune activation, inhibitors may disrupt tight junctions and cell-cell adhesion, leading to compromised barrier function and bacterial translocation[53].

10.3.2. Increased Intestinal Permeability

Disrupted barrier integrity allows luminal bacteria and toxins to enter tissues, triggering immune activation and systemic inflammation. This can exacerbate IBD and, in severe cases, cause systemic complications. Effects depend on inhibitor type, dose, and inflammatory context[53].

10.3.3. Balancing Inflammation and Barrier Integrity

Therapeutic use requires balancing anti-inflammatory benefits with barrier preservation [53]. Combining inhibitors with agents that support IEC function may mitigate barrier disruption. Hypoxia-inducible factors (HIFs) strengthen tight junctions and mucosal healing, offering a potential strategy to counteract disruption[62.]

10.4. Limited Clinical Evidence

10.4.1. Reliance on Preclinical Studies

Most evidence derives from preclinical colitis models, which do not fully capture the complexity of human IBD[59]. Although promising, findings may not directly translate, underscoring the need for cautious interpretation.

10.4.2. Need for Human Data

Further trials should assess efficacy, safety, clinical outcomes, endoscopic findings, and inflammatory biomarkers[57]. Long-term monitoring of adverse events is essential to ensure benefit-risk balance in IBD management.

11. EMERGING APPROACHES AND FUTURE DIRECTIONS OF PROTEASOME INHIBITION IN IBD

Emerging approaches and future directions in proteasome inhibition for inflammatory bowel disease (IBD) focus on enhancing specificity, minimizing systemic toxicity, and improving targeted delivery, while exploring combination therapies and novel molecular targets.

11.1 Selective Immunoproteasome Inhibition

Targeting the immunoproteasome, an inducible form prevalent in immune cells during inflammation, is a promising strategy to reduce off-target effects seen with conventional proteasome inhibitors. Recent studies highlight immunoproteasome-specific inhibitors that effectively reduce colitis severity in preclinical models by suppressing pro-inflammatory cytokines like TNF-α and IL-1β without affecting the constitutive proteasome, thus potentially lowering systemic toxicity[59,74]. Future clinical

translation requires selective agents with high subunit specificity to avoid adverse effects arising from broad proteasome inhibition[73].

11.2 Nanoparticle and Targeted Delivery Systems

Emerging drug delivery technologies such as nanoparticles and liposomes are being developed to localize proteasome inhibitors directly to the inflamed intestinal mucosa. This localized delivery enhances therapeutic efficacy and reduces systemic exposure and associated side effects, a major limitation of current therapies[62]. Utilizing bioengineered carriers or conjugates that target intestinal epithelial or immune cells could improve drug accumulation at disease sites, optimizing dose and safety.

11.3 Combination Therapies

Integrating proteasome inhibitors with existing medications like TNF inhibitors, corticosteroids, or newer small molecules (e.g., JAK inhibitors) is being explored to achieve synergistic anti-inflammatory effects while potentially lowering individual drug dosages to decrease toxicity [57,72]. Natural compounds such as apocynin, with anti-inflammatory properties and a favorable safety profile, have shown promise in preclinical colitis models, suggesting adjunct options to proteasome inhibition[74].

11.4 Modulation of Hypoxia Pathways

Stabilizing hypoxia-inducible factors (HIFs) has emerged as a novel therapeutic concept. HIF-1α stabilization improves intestinal barrier function and modulates immune responses, offering a complementary or alternative avenue to proteasome inhibition by promoting mucosal healing without systemic immunosuppression[62].

11.5 Addressing Resistance Mechanisms

Cellular resistance via alternative protein degradation pathways such as autophagy may limit proteasome inhibitors' long-term effectiveness. Combining proteasome inhibitors with autophagy or lysosomal pathway modulators could overcome resistance, enhancing treatment durability[75].

11.6 Exploration of Protease Inhibitors Beyond the Proteasome

Given the gastrointestinal tract's exposure to deregulated protease activity, natural protease inhibitors (e.g., Bowman-Birk inhibitors from legumes) are under evaluation for their anti-inflammatory and chemopreventive properties, potentially expanding the therapeutic arsenal in IBD[76].

11.7 Repurposing and Molecular Target Expansion

The role of proteasome inhibition intersects with broad cellular pathways including NF-κB, MAPK, and unfolded protein response (UPR). Emerging therapeutic strategies repurpose existing drugs or develop small molecules targeting these interconnected signaling networks to modulate intestinal inflammation more comprehensively[77,78].

11.8 Clinical Trials and Safety Assessment

Although preclinical findings are encouraging, limited clinical trials of proteasome inhibitors in IBD restrict conclusive efficacy and safety evaluations. Ongoing efforts emphasize carefully designed trials to assess therapeutic windows, long-term safety, and personalized approaches based on patient biomarker profiling[57,61].

Future proteasome inhibition in IBD therapeutics aims to increase target specificity, improve local delivery, combine therapies to maximize efficacy and minimize toxicity, and address resistance mechanisms. Synergistic approaches involving proteasome inhibitors, hypoxia pathway modulators, and natural protease inhibitors hold promise for improved management of IBD. Clinical translation

will depend on advancing selective inhibitors and personalized medicine strategies to optimize benefits while minimizing risks[59,74,75].

12. CONCLUSION

Proteasome inhibition, particularly through selective immunoproteasome targeting, offers a promising strategy for the treatment of inflammatory bowel disease by modulating key inflammatory pathways such as NF-κB and reducing pro-inflammatory cytokine production. Preclinical studies demonstrate its potential to alleviate colitis while minimizing systemic toxicity. Future research should focus on improving inhibitor selectivity, developing targeted delivery systems, and evaluating combination approaches with existing therapies. Clinical trials incorporating biomarker-driven patient selection are essential to establish optimized dosing and safety, ultimately positioning immunoproteasome inhibition as a viable therapeutic option for patients refractory to conventional treatments.

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