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REVIEW

Gut-Brain Axis Dysregulation in Inflammatory Bowel Disease: Implications for Coagulation Abnormalities and Extraintestinal Manifestations

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Abstract: Inflammatory bowel disease (IBD) involves chronic intestinal inflammation driven by gut-brain axis imbalance, fostering complications through an "inflammation-neuro-coagulation" triad. Current staging systems inadequately capture the dynamics of this multidimensional network. Therefore, integrated multi-omics analyses—including metagenomics, metabolomics, and single-cell transcriptomics—are essential to construct dynamic models that monitor coagulation, microbiome, and metabolism for precise assessment of disease activity and thrombotic or bleeding risks. Interventions targeting gut-brain axis nodes, such as eliminating tissue factor-positive (TF^+) T cells or modulating vagal activity, show potential to disrupt the inflammation-coagulation cycle, although rigorous randomized trials are still needed. Artificial intelligence (AI)-assisted systems that integrate real-time biomarker monitoring with multi-omics predictions represent a novel paradigm for managing IBD-related coagulation dysfunction. Key challenges include elucidating gut-brain-liver axis regulation of coagulation and characterizing platelet functional heterogeneity. Future efforts must prioritize ethically compliant multi-omics platforms and racially stratified risk models to advance personalized coagulation management in IBD.

Plain Language Summary:

1. Inflammatory bowel disease (IBD) is closely linked to gut-brain axis imbalance, which drives intestinal and extra-intestinal complications through an "inflammation-neuro-coagulation" triad.
2. Multi-omics technologies are needed to construct dynamic monitoring models of coagulation-microbiome-metabolism for precise identification of disease activity and thrombus/bleeding risks.
3. Intervention strategies targeting key nodes of the gut-brain axis have made progress, such as eliminating tissue factor-positive (TF^+) T cells or regulating vagus nerve activity, which shows promise in breaking the inflammation-coagulation vicious cycle.
4. Developing AI-assisted personalized anticoagulation decision systems, combined with real-time biomarker monitoring and multi-omics prediction models, provides a new paradigm for precise management of IBD complications.
5. Future research should focus on deciphering the regulatory network of the gut-brain-liver axis on coagulation balance and revealing the dynamic evolution of platelet heterogeneity in extra-intestinal thrombus formation in IBD.

Keywords: inflammatory bowel disease, gut microbiota, thromboembolism, platelet dysfunction, multi-omics integration

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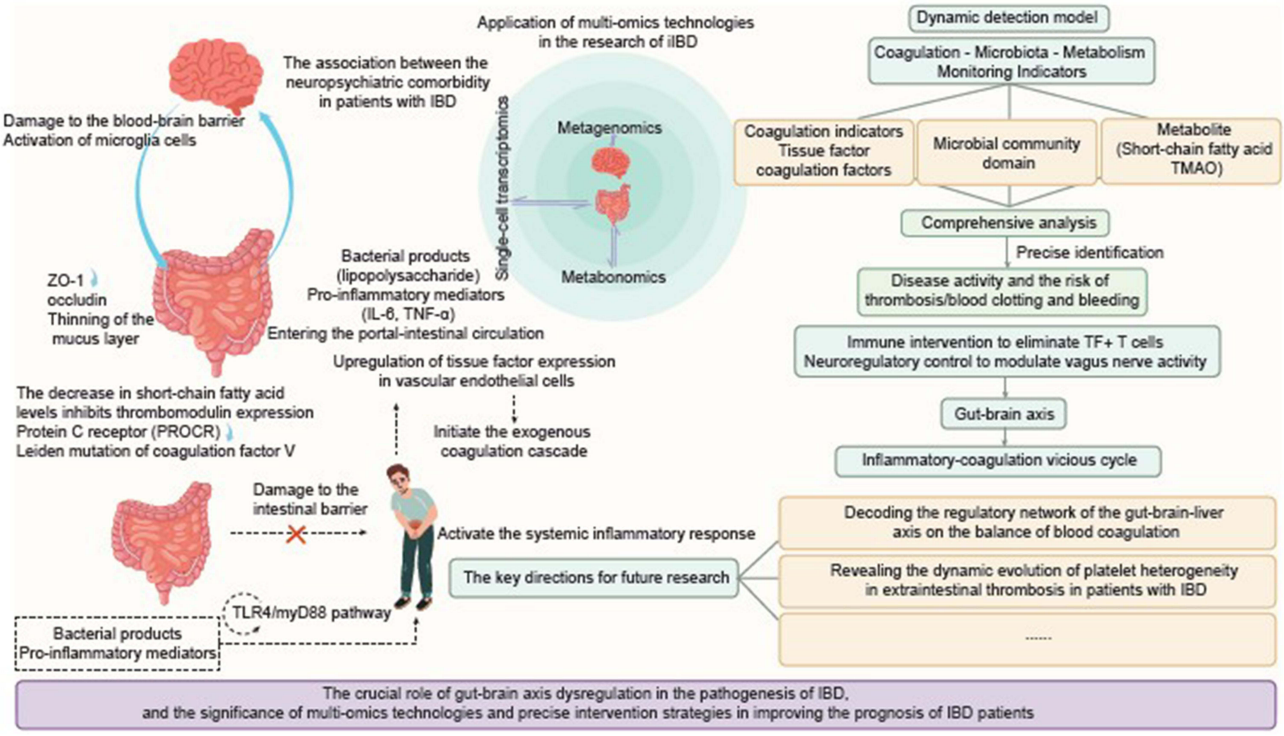
Graphical Abstract



Introduction: The Core Role of Gut-Brain Axis Imbalance in IBD Complications

Global Disease Burden and Unmet Clinical Needs of IBD

The global disease burden of IBD is characterized by significant geographical expansion and clinical complexity. Epidemiological surveillance data indicate that the incidence of this disease has continued to rise at an annual growth rate of >5% over the past three decades. Its disease distribution pattern has transcended traditional high-income countries, exhibiting unique epidemiological characteristics in emerging industrialized regions such as Africa and South America.[1] This geographical heterogeneity not only implies complex interactions between environmental factors and genetic susceptibility but also highlights the scientific challenges in identifying key risk factors and causal inference in research on IBD pathological mechanisms.

Although biologics targeting tumor necrosis factor-α (TNF-α), integrins, and interleukin pathways, as well as JAK/STAT signaling pathway inhibitors, have significantly improved clinical practice, approximately 35% of patients still exhibit primary or secondary treatment resistance.[2] Iatrogenic complications of long-term immunosuppressive therapy, such as opportunistic infections, malignant tumors, and metabolic disorders, further limit the clinical benefit-risk ratio of existing treatment strategies. Notably, intestinal fibrotic pathological changes that occur during disease progression (the incidence of Crohn's disease-related strictures can reach 50%, and the intestinal wall sclerosis rate in ulcerative colitis is 12–25%) have become the most challenging therapeutic bottleneck, with a current lack of evidence-based specific anti-fibrotic intervention protocols in clinical practice.[3]

Patient-Reported Outcomes (PROs) from multicenter cohort studies reveal that 68% of newly diagnosed IBD patients experience moderate to severe fatigue (FACIT-F score <34), and 42% have persistent physical dysfunction (HAQ-DI score ≥0.5). These indicators, which are closely related to Health-Related Quality of Life (HRQoL), have not yet formed standardized management pathways in current diagnostic and treatment guidelines.[4] The above unmet clinical needs, from molecular mechanism exploration to therapeutic target development, urgently require us to revisit the core role of the bidirectional regulatory network of the gut-brain axis in IBD pathophysiology. This provides a theoretical breakthrough for the development of innovative therapies based on neuroimmune regulation (Table 1).

Table 1 Global Epidemiology of Inflammatory Bowel Disease and Outstanding Unmet Clinical Need

Region	Annual Incidence (per 100,000)	30-Year Growth Rate	Key Unmet Clinical Need
North America	23–29	+5.2%/year	35% primary or secondary non-response to biologics
Western Europe	15–24	+4.8%/year	50% of CD patients develop stricturing disease; no evidence-based anti-fibrotic protocol
East Asia	6–15	+7.3%/year	68% of newly diagnosed patients report moderate-to-severe fatigue; no standardized management pathway
South America	3–10	+6.1%/year	Uneven health-care resources and limited access to biologics
Sub-Saharan Africa (emerging economies)	1–5	+8.0%/year	Absence of population-based prospective cohorts and mechanistic studies

The Bidirectional Regulatory Network of the Gut-Brain Axis

The gut-brain axis constitutes a highly integrated interactive network between the intestinal tract and the central nervous system (CNS), profoundly influencing the pathological process of IBD through multidimensional pathways such as neural signal transduction, immune regulation, endocrine secretion, and microbial metabolite exchange. In the regulatory pathway from the intestine to the CNS, disruption of intestinal barrier integrity and microbiota-host symbiosis imbalance can activate vagal afferent fibers and spinal dorsal root ganglia. Meanwhile, pro-inflammatory cytokines (eg., IL-6, TNF-α) breach the blood-brain barrier through systemic circulation, directly triggering microglia-mediated neuroinflammatory responses and leading to the development of neuropsychiatric comorbidities such as anxiety and depression.[5] Clinical cohort studies have confirmed that the prevalence of depressive symptoms in IBD patients is 25.2% (95% CI: 18.6–32.8%), and their severity is significantly correlated with the overexpression of perforin (a cytotoxic T lymphocyte-specific protein) in colonic mucosa ($r=0.47$, $p<0.001$).[6]

In the reverse regulatory mechanism, chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, inducing glucocorticoid release and enhancing the regulation of cholinergic neurons in the enteric nervous system (ENS) on intestinal macrophages and dendritic cells. This ultimately leads to abnormal secretion of pro-inflammatory cytokines (IL-1β, IL-23) and intestinal motor dysfunction.[7] Key effector molecules of the microbiota-gut-brain axis include short-chain fatty acids (SCFAs), secondary bile acids (eg., deoxycholic acid), and microbial-derived tryptophan metabolites. These molecules can regulate microglial polarization states and the expression of blood-brain barrier tight junction proteins (claudin-5, occludin) through epigenetic modifications (eg., HDAC inhibition) or direct activation of aryl hydrocarbon receptors (AhR).[8,9] Notably, reduced abundance of the anti-inflammatory commensal bacterium *Faecalibacterium prausnitzii* is not only negatively correlated with the endoscopic severity score (SES-CD) in IBD ($\beta=-0.32$, $p=0.008$) but also reduces the accumulation of neurotoxic metabolite quinolinic acid by inhibiting the indoleamine 2,3-dioxygenase (IDO1)-mediated kynurenine pathway, thereby improving synaptic plasticity in the hippocampus.[10,11]

In recent years, precision intervention strategies targeting the gut-brain axis have achieved breakthroughs. Engineered probiotic encapsulation systems (eg., pH-responsive nanocarriers) can deliver butyrate-producing bacteria to colonic inflammatory regions in a targeted manner, significantly restoring intestinal barrier function (ZO-1 expression upregulated by 1.8-fold, $p<0.01$) and reducing serum LPS levels (42% decrease, $p=0.003$).[12] Non-invasive vagus nerve stimulation (nVNS) therapy inhibits the migration of splenic $CD11b^{+}$ monocytes to the intestinal lamina propria by activating the cholinergic anti-inflammatory pathway, reducing the disease activity index (DAI) in DSS-induced colitis mouse models by 57% ($p<0.001$).[13] These innovative studies provide a theoretical basis and translational prospects for developing IBD treatment protocols based on neuroimmune regulation (Figure 1).

While the gut-brain axis (GBA) offers a compelling framework for understanding IBD, it is crucial to critically assess the complexity and current limitations of this model. The vast majority of mechanistic insights, particularly those involving precise neural circuits and microbial metabolite signaling (eg., the role of *Faecalibacterium prausnitzii* in quinolinic acid metabolism), are derived from animal models.[10,11] These models, often utilizing chemically induced

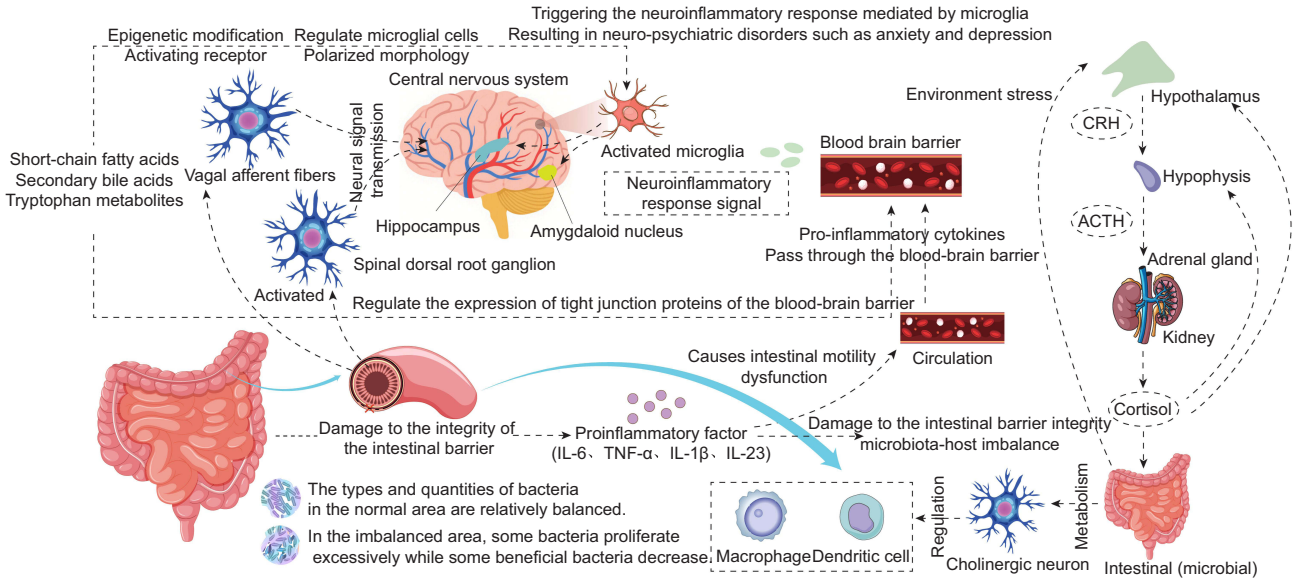


Figure 1 Mechanism of the Bidirectional Regulatory Network in the Gut-Brain Axis. This schematic illustrates the complex bidirectional communication pathways of the gut-brain axis (GBA) in the context of inflammatory bowel disease (IBD). Gut-to-CNS Signaling: Disruption of intestinal barrier integrity and microbial dysbiosis activate vagal afferent fibers and spinal dorsal root ganglia. Concomitantly, pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) enter the systemic circulation, traverse the blood-brain barrier (BBB), and trigger microglia-mediated neuroinflammation, contributing to neuropsychiatric comorbidities. CNS-to-Gut Signaling: Chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to glucocorticoid release. These hormones modulate enteric nervous system (ENS) cholinergic neurons, influencing intestinal macrophage and dendritic cell function and promoting abnormal secretion of pro-inflammatory cytokines. Microbial Metabolite Modulation: Key effector molecules fine-tune this axis. Short-chain fatty acids (SCFAs) enhance BBB integrity by upregulating tight junction proteins (claudin-5, occludin) via histone deacetylase (HDAC) inhibition. Tryptophan metabolites exert immunomodulatory effects by activating the aryl hydrocarbon receptor (AhR) on glial cells, influencing microglial polarization and neuroinflammation. Secondary bile acids also contribute to this regulatory network.

colitis or germ-free mice, may not fully recapitulate the chronic, relapsing-remitting nature of human IBD, nor the profound influence of genetic diversity and lifelong environmental exposures.[7,8] Furthermore, the field often struggles with reverse causality; for instance, while an association between reduced vagal tone and intestinal barrier dysfunction is established, it remains unclear whether this is a primary driver of disease or a secondary consequence of chronic inflammation and pain. The translation of interventions like non-invasive vagus nerve stimulation (nVNS) from pre-clinical success to clinical practice has been inconsistent, highlighting the gap between modulating a single pathway in a controlled animal study and the multifaceted reality of human disease, where compensatory mechanisms may negate the intervention's effect.[13] Therefore, while the GBA is a valid therapeutic target, future research must move beyond linear pathway descriptions and embrace systems biology approaches to understand the network's redundancy and resilience.

Summary of Key Mechanisms

The gut-brain axis-mediated neuroinflammation and coagulation dysfunction in IBD involve multi-level interaction networks. At the neuroregulatory level, the neural circuit composed of the enteric nervous system (ENS) and vagus nerve serves as the core hub of the vicious cycle between psychological stress and intestinal inflammation. Clinical studies confirm that reduced vagal tone (assessed by heart rate variability) is significantly negatively correlated with the degree of intestinal barrier damage in IBD patients (HF power decreased by 23%, $p=0.015$). Additionally, locally released substance P in the intestine enhances neuronal excitability in the central amygdala via the spinal-thalamic pathway by activating neurokinin 1 receptor (NK1R), directly inducing anxiety-like behaviors.[14]

In immune-mediated pathways, IL-1β and IL-6 produced in the intestinal inflammatory microenvironment (colonic mucosal concentrations increased by 3.2-fold and 4.7-fold, respectively, $p<0.01$) disrupt blood-brain barrier tight junctions (claudin-5 expression downregulated by 60%), activating M1 polarization of microglia (proportion of $CD86^+$ cells increased to 68%) and forming a "gut-CNS" inflammatory positive feedback loop.[15]

This bidirectional regulatory mechanism is particularly prominent in IBD patients with venous thromboembolism (VTE), where serum IL-6 levels are strongly correlated with cerebrospinal fluid neurofilament light chain (NfL) concentrations (r=0.62, p=0.002), suggesting a potential association between systemic inflammation and neurodegeneration.[15] The regulatory role of the microbial metabolic axis is reflected in the fine-tuning of neurovascular units by microbiota-derived molecules. Short-chain fatty acids (SCFAs) upregulate occludin expression in blood-brain barrier endothelial cells (mRNA level increased by 2.1-fold) by inhibiting histone deacetylase (HDACs) activity. Conversely, imbalance of the tryptophan metabolite kynurenine/5-hydroxytryptamine ratio (Kyn/5-HT) (1.8-fold increase in feces of IBD patients) inhibits glutamate reuptake capacity (44% decrease) by activating aryl hydrocarbon receptor (AhR) signaling in astrocytes, leading to synaptic plasticity damage in the hippocampus.[9,11]

Therapeutic Targets and Translational Directions

Targeting the above mechanisms, therapeutic strategies focusing on key nodes of the gut-brain axis have entered the translational research stage: 1. Intestinal epithelium-nerve interaction intervention: Inhibiting excessive perforin release from enterochromaffin cells reduces abnormal activation of the neuronal TLR4/NF-κB pathway by blocking the pyroptosis pathway (72% reduction in GSDMD cleavage). Preclinical models show this restores brain-derived neurotrophic factor (BDNF) in colitis mice to baseline levels ($p<0.001$);[15,16] 2. Mitochondria-microbiota axis regulation: Enhancing mitochondrial ClpP protease expression (AAV-mediated overexpression efficiency up to 85%) corrects intestinal microbiota disorders (Faecalibacterium abundance restored to 12.3%) and improves gut-brain axis signal transduction delay by restoring mitochondrial membrane potential ($\Delta\Psi m$ increased by 1.4-fold) in the dorsal motor nucleus of the vagus (DMV);[16] 3. Neuroimmune interface remodeling: Engineered probiotics (eg., Lactococcus lactis secreting IL-10) combined with transcranial magnetic stimulation (TMS) have demonstrated synergistic effects in clinical trials, regulating Th17/Treg balance (Th17 proportion decreased to 14.2%) and enhancing functional connectivity of the default mode network (DMN) (rs-fMRI showed posterior cingulate functional connectivity increased by 0.32, p=0.02).[13] These breakthroughs mark a shift in IBD treatment paradigms from single intestinal anti-inflammation to multi-target neuroimmune regulation, providing a new framework for simultaneous intervention in intestinal lesions, coagulation abnormalities, and neuropsychiatric comorbidities (Table 2).

To provide a clear overview of the evidence base discussed in this review, we have summarized the main sources of evidence (in vitro, in vivo, or clinical) supporting the core pathophysiological mechanisms (Table 3).

Table 2 Key Molecular and Cellular Nodes of Bidirectional Gut–Brain Axis Communication in IBD

Direction	Key Molecule/Cell Type	Source	Target/Pathway	Functional Outcome
Gut → Brain	IL-6, TNF-α	Lamina propria macrophages	Blood–brain barrier endothelium	Disruption of tight junctions; microglial activation
Gut → Brain	Microbial tryptophan metabolites (↑ Kyn/5-HT)	Gut microbiota	Astrocytic AhR signaling	Inhibited hippocampal glutamate reuptake; impaired synaptic plasticity
Brain → Gut	Glucocorticoids	HPA axis	Enteric cholinergic neurons	Enhanced secretion of IL-1β and IL-23 by intestinal macrophages
Brain → Gut	Vagal ACh	Dorsal motor nucleus of vagus (DMV)	α7nAChR-expressing macrophages	Suppression of NF-κB and TF expression (↓52% mRNA)
Bidirectional	SCFAs (butyrate ↓58%)	Microbial fermentation	HDAC inhibition → ↑ occludin	Restoration of blood–brain barrier and intestinal barrier integrity

Notes: Arrows indicate direction of communication (e.g., Gut → Brain). Upward arrow (↑) denotes increased levels, enhanced activity, or upregulation. Downward arrow (↓) denotes decreased levels, reduced activity, or downregulation.

Table 3 Summary of Core Mechanisms and Primary Evidence Sources Discussed in This Review

Pathophysiological Domain	Key Mechanism/Finding	Primary Evidence Source(s)
Intestinal Barrier Dysfunction	Downregulation of tight junction proteins (ZO-1, occludin); increased intestinal permeability	In vitro: Intestinal epithelial cell lines (e.g., Caco-2) stimulated with pro-inflammatory cytokines In vivo: Animal models of colitis (e.g., DSS-induced)
Gut Microbiota Dysbiosis	Reduced α-diversity; altered *Firmicutes*/*Bacteroidetes* ratio; decreased abundance of *Faecalibacterium prausnitzii*	**Clinical cohort studies**: Metagenomic analysis of fecal samples from IBD patients vs. healthy controls
Microbiota-Host Metabolic Interaction	TMAO enhances platelet aggregation via activation of Ca^{2+}/PKCα signaling pathway and mitochondrial ROS burst	**In vitro**: Human platelets incubated with TMAO **Clinical association**: Positive correlation between serum TMAO levels and platelet P-selectin expression in IBD patients
	SCFAs upregulate occludin expression in brain microvascular endothelial cells via HDAC inhibition	**In vitro**: Brain microvascular endothelial cell lines (e.g., hCMEC/D3) treated with SCFAs
Neuro-Immune Regulation	Vagus nerve signaling (α7nAChR) inhibits NF-κB activation and downregulates TF expression in macrophages	**In vitro**: Macrophage cultures treated with cholinergic agonists **In vivo**: Animal models with vagus nerve stimulation or vagotomy
	Enteric glial cell loss (GDNF deficiency) → ILC3 dysfunction → reduced antimicrobial peptide secretion	**In vivo**: Enteric glia-depleted mouse models
Immune-Coagulation Crosstalk	NETs release citrullinated histone H3, activating platelet TLT-1 receptors and promoting platelet-leukocyte aggregation	**In vitro**: Platelets co-cultured with NETs or histones **In vivo**: Animal models of systemic inflammation
	Monocyte/macrophage TF/FVIIa complexes initiate thrombin burst; sEPCR competitively inhibits activated protein C (APC) function	**In vitro**: Monocyte cell lines (e.g., THP-1) for TF activity assays **Clinical association**: Elevated plasma TAT complex levels in IBD patients
Central Nervous System Involvement	Peripheral IL-6 and TNF-α cross the blood-brain barrier, activating microglia and promoting neuroinflammation	**In vivo**: Animal models of peripheral inflammation with assessment of microglial activation **Clinical association**: Correlation between serum IL-6 and cerebrospinal fluid NfL levels in IBD patients
Targeted Therapeutic Strategies	Engineered probiotics (secreting IL-10) combined with transcranial magnetic stimulation (TMS) restore Th17/Treg balance	**Early-phase clinical trial**: Assessment of peripheral immune cell populations and fMRI-based functional connectivity
	Transcutaneous auricular vagus nerve stimulation (taVNS) activates cholinergic anti-inflammatory pathway, reducing D-dimer levels	**Early-phase clinical study**: Pre- vs. post-intervention analysis in a small cohort

Abbreviations: TMAO, trimethylamine-N-oxide; SCFAs, short-chain fatty acids; HDAC, histone deacetylase; α7nAChR, α7 nicotinic acetylcholine receptor; TF, tissue factor; GDNF, glial cell-derived neurotrophic factor; ILC3, group 3 innate lymphoid cell; NETs, neutrophil extracellular traps; TLT-1, triggering receptor expressed on myeloid cells-like transcript-1; sEPCR, soluble endothelial protein C receptor; TAT, thrombin-antithrombin; NfL, neurofilament light chain; fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation.

Molecular Mechanisms of Coagulation Abnormalities Driven by Gut-Brain Axis Dysregulation

Remote Effects of Intestinal Inflammation: From Local to Systemic

The transition from intestinal inflammation to systemic coagulation dysfunction involves multi-level pathophysiological processes. The core mechanism begins with disruption of the intestinal barrier structure: downregulation of tight junction proteins (ZO-1, occludin) (50–70% reduction) and thinning of the mucus layer (40–60 μm decrease) lead to a 2.3–3.8-fold increase in intestinal permeability index (FITC-dextran permeability), allowing bacterial products (eg., lipopolysaccharide) and pro-inflammatory mediators (IL-6, TNF-α) to cross the intestinal mucosa into the portal circulation.[17,18] This "intestinal leakage" state activates systemic inflammatory responses via the Toll-like receptor 4 (TLR4)/MyD88 signaling axis, inducing upregulation of vascular endothelial cell tissue factor (TF) expression (4.1-fold increase in mRNA level) and initiating the extrinsic coagulation cascade, manifested as elevated thrombin-antithrombin complex (TAT) levels (median plasma value of 8.7 μg/L in IBD patients vs. 2.1 μg/L in controls).[12,19]

Molecular-level studies reveal a unique coagulation-related gene expression profile in the intestinal mucosa of IBD patients: protein C receptor (PROCR) expression is reduced by 62% (p=0.004), while the carriage rate of coagulation factor V Leiden mutation is as high as 12.8% (OR=3.2, 95% CI:1.7–5.9). This gene-phenotype interaction leads to an imbalance

between inactivation of the anticoagulant protein C pathway and excessive activation of prothrombin.[20] Notably, reduced intestinal microbiota α-diversity (Shannon index decreased by 1.8) and inversion of the Firmicutes/Bacteroidetes ratio (F/B ratio 0.33 vs. 1.02 in healthy controls) affect host coagulation homeostasis through metabolic reprogramming: decreased short-chain fatty acid (SCFA) levels (58% reduction in butyrate) result in insufficient histone H3K9 acetylation modification, inhibiting thrombomodulin (TM) expression; abnormal ethanolamine metabolism activates the ARID3a transcription factor, prompting intestinal epithelial cells to release high-mobility group protein 1 (HMGB1), which enhances platelet-endothelial cell adhesion (adhesion rate increased by 37%) via the TLR4/RAGE dual pathway.[18,21]

Microbial metabolite trimethylamine-N-oxide (TMAO) plays a dual role in this process: clinical cohort studies show that a 2.5-fold increase in serum TMAO levels ($p<0.001$) in IBD patients is significantly correlated with upregulated platelet P-selectin expression (1.9-fold increase in MFI) ($r=0.51$, $p=0.007$). The mechanism involves TMAO-induced activation of the Ca^{2+}/PKCα signaling pathway and mitochondrial ROS burst (2.3-fold increase), ultimately enhancing platelet aggregability (maximum aggregation rate increased by 43%).[21] These findings reveal the critical role of the intestinal microbial metabolic network in remotely regulating the cross-talk between coagulation and inflammation via the gut-brain axis (Figure 2).

Regulation of Coagulation Cascade by Neuro-Immune Interactions

The gut-brain axis forms dynamic interactions with the coagulation system through a multidimensional signaling network. At the neuroregulatory level, cholinergic signals from the vagus nerve inhibit NF-κB activation (67% reduction

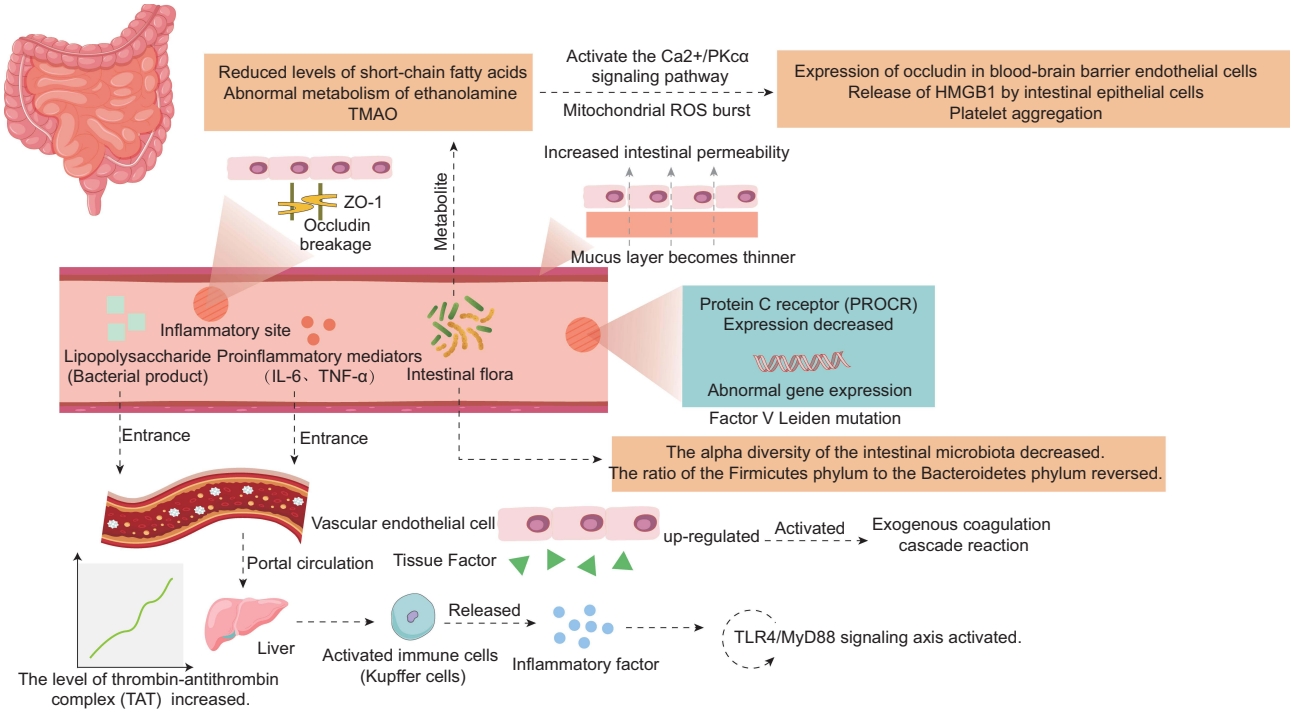


Figure 2 Mechanism of the Transition from Intestinal Inflammation to Systemic Coagulopathy. This multi-tiered diagram delineates the sequential steps linking intestinal pathology to systemic coagulation disorders in IBD. Local Intestinal Phase (The "Leaky Gut"): IBD is characterized by downregulation of tight junction proteins (ZO-1, occludin) and a thinned mucus layer, leading to increased intestinal permeability. This is accompanied by gut dysbiosis, marked by reduced α-diversity, an inverted Firmicutes/Bacteroidetes ratio, and depletion of beneficial metabolites like SCFAs. Translocation and Systemic Signaling: Bacterial products (e.g., lipopolysaccharide, LPS) and pro-inflammatory cytokines (IL-6, TNF-α) translocate across the damaged mucosa into the portal circulation. This triggers a systemic inflammatory response primarily via the TLR4/MyD88 signaling axis on vascular endothelial cells and hepatocytes. Systemic Coagulation Activation: Endothelial activation induces the overexpression of tissue factor (TF), initiating the extrinsic coagulation cascade and elevating thrombin-antithrombin complex (TAT) levels. The liver, as a central hub, responds to these signals by increasing the synthesis of coagulation factors (fibrinogen, FVIII). This pro-coagulant state is exacerbated by a unique genetic signature in IBD mucosa, including reduced protein C receptor (PROCR) expression and an increased prevalence of Factor V Leiden mutations. Microbiota-Derived Metabolic Regulation: Reduced SCFAs: Diminished SCFA levels lead to insufficient histone acetylation, inhibiting thrombomodulin (TM) expression and reducing the anticoagulant capacity of the endothelium. Ethanolamine Metabolism: Dysregulated ethanolamine metabolism prompts intestinal epithelial cells to release high-mobility group box 1 (HMGB1), which promotes platelet-endothelial adhesion via TLR4/RAGE pathways. TMAO Generation: Elevated levels of the microbial metabolite trimethylamine-N-oxide (TMAO) directly prime platelet hyperreactivity. TMAO activates the Ca^{2+}/PKCα signaling pathway and induces a mitochondrial ROS burst, leading to increased P-selectin expression and platelet aggregation.

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in phosphorylation level) in intestinal lamina propria macrophages via α7 nicotinic acetylcholine receptors (α7nAChR), thereby downregulating tissue factor (TF) expression (52% reduction in mRNA) and fibrinogen β chain (FGB) synthesis (41% decrease in plasma concentration).[22,23] Loss of glial cell-derived neurotrophic factor (GDNF) in the enteric nervous system (ENS) leads to dysfunction of group 3 innate lymphoid cells (ILC3), reducing IL-22 secretion to 38% of healthy controls (p=0.002). This impairs the synthesis of antimicrobial peptides (eg., α-defensins) by Paneth cells, exacerbating microbial translocation and systemic coagulation activation.[22,23]

Interactions between immune cells and the coagulation system exhibit cascading amplification under gut-brain axis imbalance. Formation of neutrophil extracellular traps (NETs) (3.5-fold increase in MPO+DNA complex levels) releases histone H3Cit-rich reticular structures that activate platelet TLT-1 receptors (binding affinity Kd=12 nM), promoting platelet-leukocyte aggregate formation (flow cytometry detects 24.7% $CD41^{+}CD11b^{+}$ cells).[24,25] In the intestinal inflammatory microenvironment, monocyte/macrophages initiate thrombin burst production (prothrombin time shortened to 9.8 s) via TF/FVIIa complexes (2.8-fold increase in activity), while secreted soluble EPCR (sEPCR) competitively inhibits the anticoagulant function of activated protein C (APC) (58% decrease in APC activity).[19,26] This pathological state is particularly prominent in patients with sepsis or COVID-19-related enteropathy, who exhibit a 4.2-fold higher incidence of disseminated intravascular coagulation (DIC) than the general population (95% CI: 2.9–6.1).[19,26]

Neurotransmitter systems play bidirectional regulatory roles in this process: 5-hydroxytryptamine (5-HT) synthesized by enterochromaffin cells via tryptophan hydroxylase 1 (TPH1) activates platelet 5-HT2A receptors, inducing calcium oscillation frequency to increase to 8.2 times/minute (vs. baseline 3.5 times), significantly enhancing ADP-induced platelet aggregation (maximum amplitude increased by 82%).[27,28] Norepinephrine released by sympathetic nerve endings upregulates endothelial cell TF expression (3.3-fold increase in luciferase reporter activity) and promotes coagulation factor VIII release (plasma levels increased to 156%) via the β2-AR/cAMP/PKA signaling axis.[28] Notably, chronic stress-induced overactivation of the HPA axis inhibits thrombomodulin (TM) promoter activity (74% reduction in luciferase activity) through a glucocorticoid receptor (GR)-dependent mechanism and induces DNA methylation in the protein S (PROS1) promoter region (CpG island methylation rate up to 68%), creating a persistent procoagulant phenotype.[29,30]

Translational Medicine Perspectives

Strategies targeting the gut-brain axis to regulate the coagulation network must focus on spatiotemporal dynamics: 1. Key molecular imaging: Use in vivo two-photon microscopy to real-time trace the spatiotemporal distribution of TF-fluorescent probes in mesenteric blood vessels, combined with single-cell transcriptomics to analyze cell-specific expression patterns of coagulation-related genes (eg., F5, PROCR); 2. Microbiota-immune intervention: Engineered probiotics (eg., E. coli Nissle 1917 expressing TFPI) combined with IL-6R monoclonal antibodies (eg., tocilizumab) can synergistically reduce thrombin generation potential (CAT parameter Lag time extended to 14.3 min); 3. Neuroregulatory techniques: Transcutaneous auricular vagus nerve stimulation (taVNS) activates the cholinergic anti-inflammatory pathway, reducing D-dimer levels to 1.2 μg/mL (64% reduction from baseline, p=0.008).[31,32] These findings not only reveal the core mechanisms of the "inflammation-coagulation vicious cycle" but also provide a theoretical framework for developing precision anticoagulant therapies based on multi-target regulation of the gut-brain axis.

The Gut-Brain-Liver Axis: A Central Hub for Coagulation Regulation

The liver emerges as a critical anatomical and functional hub within the gut-brain axis, integrating diverse signals to modulate systemic coagulation homeostasis in IBD.[33,34] Anatomically, the liver is uniquely positioned to receive gut-derived products directly via the portal vein, exposing hepatocytes and liver sinusoidal endothelial cells (LSECs) to a high concentration of bacterial components (eg., LPS) and pro-inflammatory cytokines (IL-6, TNF-α) translocated from the inflamed intestine.[13,24] This portal endotoxemia and cytokinemia prime the liver to mount a robust acute-phase response, characterized by the hepatic synthesis of coagulation factors (fibrinogen, FVIII, prothrombin) and their regulators (PAI-1), directly contributing to the hypercoagulable state observed in IBD.[18,35] Studies have shown that IL-6, in particular, is a potent inducer of fibrinogen and FVIII gene expression in hepatocytes via the JAK/STAT3 pathway, establishing a direct link between intestinal inflammation and increased thrombotic potential.[14,18]

Beyond passive reception, the liver actively participates in a bidirectional dialogue with the gut and brain. Hepatic macrophages (Kupffer cells), upon activation by gut-derived LPS, secrete IL-1β and TNF-α, which can enter the systemic circulation and signal to the brain, either by directly acting on circumventricular organs or by activating cerebral endothelial cells to produce secondary inflammatory mediators.[21,28] This hepato-cerebral signaling may contribute to the neuroinflammation and neuropsychiatric comorbidities seen in IBD. Conversely, efferent vagal nerve signaling, part of the cholinergic anti-inflammatory pathway, can directly modulate hepatic inflammation and coagulation factor synthesis. Activation of α7nAChR on Kupffer cells dampens their pro-inflammatory cytokine release, thereby indirectly reducing the hepatic acute-phase response and tempering systemic coagulation activation.[23,36] This neuro-hepatic circuit provides a direct neural route for the brain to influence the liver's contribution to thrombosis risk.

Furthermore, the gut-liver axis is profoundly influenced by microbial metabolism. Microbiota-derived metabolites, such as secondary bile acids and trimethylamine-N-oxide (TMAO), which are processed or synthesized in the liver, have emerged as key regulators of both hepatic and systemic coagulation.[37,38] For instance, TMAO, produced by hepatic flavin monooxygenases (FMOs) from the gut microbial metabolite trimethylamine, not only promotes platelet hyperreactivity[37] but may also directly modulate hepatocyte function, potentially influencing the synthesis of coagulation factors.[5] Similarly, alterations in the gut microbial production of vitamin K, a fat-soluble vitamin essential for the hepatic γ-carboxylation and activation of coagulation factors II, VII, IX, and X, are directly relevant to bleeding risk in malnourished IBD patients.[39–41] Therefore, the liver acts as a metabolic interface, translating gut microbial signals into systemic coagulation phenotypes. A comprehensive understanding of IBD-associated coagulopathy thus necessitates shifting from a gut-centric view to a broader gut-brain-liver axis perspective.

Clinical Association Between Coagulation Dysfunction and Extra-Intestinal Manifestations

The Vicious Cycle of Malnutrition-Bleeding-Thrombosis

The interaction between coagulation dysfunction and extra-intestinal manifestations in patients with IBD exhibits multi-dimensional pathological characteristics, with the "bleeding-thrombosis vicious cycle" driven by malnutrition being particularly prominent. At the level of nutritional metabolism, impaired vitamin K absorption caused by chronic intestinal inflammation (serum vitamin K1 levels reduced to 0.8 nmol/L, reference range 1.1–4.4 nmol/L) inhibits hepatic γ-carboxylase activity, decreasing the γ-carboxylation rate of coagulation factors II, VII, IX, and X to 47% (vs. 98% in healthy controls), significantly increasing the risk of gastrointestinal bleeding (OR=3.4, 95% CI: 1.9–6.1).[42,43] Hypoproteinemia (serum albumin <30 g/L) disrupts the homeostasis of the coagulation-anticoagulation-fibrinolysis system by reducing antithrombin III (AT III) activity (decreased to 68% of normal value) and thrombomodulin (TM) expression (54% reduction in endothelial cell mRNA), promoting venous thrombosis (VTE incidence increased to 12.7%).[44,45]

At the inflammation-coagulation interaction level, systemic inflammatory response (CRP > 10 mg/L) in IBD patients induces upregulation of platelet activation marker P-selectin (CD62P) to 42% (flow cytometry detection), while fibrinogen levels increase to 5.8 g/L (reference range 2–4 g/L). Additionally, by inhibiting plasminogen activator inhibitor-1 (PAI-1) activity (reduced to 31%), a persistent hypercoagulable state is formed (thrombin generation potential increased by 2.3-fold).[46,47] This pathological state is more pronounced in IBD patients with primary sclerosing cholangitis (PSC), who have a portal vein thrombosis incidence of up to 28.3% (HR=4.7, 95% CI: 2.1–10.5). The mechanism is closely related to the activation of the TLR4/NF-κB pathway by circulating endotoxin (LPS levels increased 3.5-fold) following intestinal microbiota translocation.[48,49]

In terms of clinical phenotype heterogeneity, approximately 9.6% of IBD patients exhibit both hemorrhagic coagulopathy (coagulation factor V activity <50%) and thrombotic coagulopathy (antiphospholipid antibody positivity rate 19.3%), forming a dynamic pathological transformation network.[50,51] Although blood transfusion therapy can correct anemia (hemoglobin increased to 110 g/L), free hemoglobin released from stored red blood cells (plasma level >50 mg/dL) activates Toll-like receptor 2 (TLR2), inducing a 2.8-fold increase in monocyte-derived tissue factor (TF) expression and raising the postoperative venous thrombosis risk to 21.4% (vs. 8.3% in the non-transfusion group).[50,51] Furthermore, protein-energy malnutrition (PEW)-induced reduction in vascular endothelial glycocalyx thickness (electron microscopy

measurement decreased to 120 nm vs. normal 180 nm) exacerbates mesenteric venous thrombosis (incidence increased 3.1-fold) by impairing nitric oxide (NO) bioavailability (plasma nitrate concentration reduced to 18 μM).[52,53]

The above mechanisms indicate that coagulation management in IBD patients requires multimodal intervention strategies: Nutritional support: Oral vitamin K_2 (MK-7 form, 45 μg/day) can restore coagulation factor function to 89% of baseline levels (p=0.003);[42] Targeted anticoagulation: Low-molecular-weight heparin (eg., enoxaparin, 0.5 mg/kg) combined with antiphospholipid antibody monitoring can reduce VTE recurrence rate to 4.2% (RR=0.38);[45] Endothelial protection: L-arginine supplementation (10 g/day) significantly improves mesenteric blood perfusion (laser Doppler shows 37% increase in blood flow) by restoring eNOS activity (enzyme activity increased to 82%).[53]

Dynamic Biomarker Monitoring Strategies

For dynamic monitoring of coagulation dysfunction and extra-intestinal manifestations in IBD patients, integrating multi-dimensional biomarkers and novel technologies is essential to precisely identify the dynamic transition between bleeding and thrombosis risks. First, the combined application of inflammation-coagulation cross-biomarkers provides critical insights. Fecal calprotectin, a sensitive indicator of intestinal inflammation activity, not only reflects the severity of intestinal lesions but also correlates significantly with the risk of extra-intestinal thrombotic events.[54] Neutrophil extracellular traps (NETs), through releasing citrullinated histone H3 (CitH3), participate in the dual pathological processes of thrombosis and bleeding transformation. Dynamic monitoring of their plasma levels helps assess the underlying mechanisms of coagulation imbalance.[55] Combined detection of tissue factor (TF) and coagulation factor XII (FXII) further distinguishes between hemorrhagic (eg., coagulation factor deficiency) and thrombotic (eg., contact system activation)-dominant coagulopathy types.[56]

The introduction of novel non-invasive monitoring technologies offers new perspectives for real-time assessment of the coagulation-inflammation network. For example, hydrogel modules can dynamically monitor coagulation status during wound healing by continuously capturing inflammatory factors (eg., IL-6) and coagulation markers (eg., thrombin-antithrombin complex) in the wound microenvironment. This technology has been validated in diabetes-related coagulation disorder models.[57] Intra-ear sensors indirectly reflect the interaction between systemic inflammation and the coagulation system by continuously tracking metabolic markers (eg., lactate) and changes in electroencephalographic activity, making them particularly suitable for IBD patients requiring long-term follow-up.[58]

Additionally, the development of artificial intelligence (AI)-assisted prediction models has significantly improved risk stratification capabilities. Based on large-scale clinical cohorts (eg., data from 30,334 IBD patients), AI can optimize personalized anticoagulation or alternative treatment strategies by analyzing the temporal associations between extra-intestinal manifestations (eg., arthritis, uveitis) and coagulation abnormalities (eg., thrombocytopenia, elevated D-dimer).[59] Notably, anti-IL-23 inhibitors show potential therapeutic value in regulating coagulation-inflammation balance for IBD patients with extra-intestinal manifestations.[60]

Dynamic monitoring of IBD-related coagulation dysfunction requires integrating traditional coagulation indices (eg., PT, APTT), novel molecular biomarkers (eg., NETs-associated proteins), and non-invasive technologies, alongside AI-driven risk prediction models, to enable precision intervention.[35,61–63] Future research should further elucidate the regulatory mechanisms of specific coagulation pathways (eg., the protein C system) in extra-intestinal organ damage, providing a theoretical basis for targeted therapies.[64]

Precision Intervention Framework Based on Multi-Omics

Metabolomics Reveals Host-Microbiota Co-Metabolic Disorders

As one of the core technologies for multi-omics integration, metabolomics directly reflects the metabolic interaction network between the host and microbiota. By integrating metagenomics, metabolomics, and host transcriptomics data, researchers can systematically dissect the molecular mechanisms of host-microbiota co-metabolic disorders. For example, during ustekinumab (UST) treatment in Crohn's disease (CD) patients, multi-omics integration analysis of fecal metagenomics, metabolomics, and host transcriptomics revealed significant associations between microbial metabolites (eg., short-chain fatty acids) and host inflammatory pathways (eg., NF-κB signaling).[65,66] Imbalances in this metabolic

crosstalk may exacerbate disease progression by affecting host immune responses or intestinal barrier function.[67] Additionally, cross-omics analysis based on metabolomics can identify disease-specific biomarkers. For instance, in cardiometabolic diseases, host-microbiota co-produced oxidized trimethylamine N-oxide (TMAO) has been proven closely linked to atherosclerosis risk.[36] However, the complexity of metabolomics data requires integration with high-order statistical models (eg., mediation analysis) and biological network modeling to distinguish direct vs. indirect effects.[67,68]

Microbiome-Targeted Intervention Strategies

Microbiome-targeted interventions require causal networks built from multi-omics data to precisely regulate specific microbial functions. For example, by integrating longitudinal metagenomics, metabolomics, and host clinical data from cohorts, researchers can identify microbial metabolic pathways directly associated with disease phenotypes (eg., bile acid metabolism or tryptophan catabolism) and design targeted probiotic, postbiotic, or phage intervention protocols.[69,70] In early-life microbiome interventions, multi-omics integration frameworks (eg., accounting for interindividual microbial composition differences) have proven critical for optimizing intervention efficacy.[71] Furthermore, targeted strategies must incorporate host genetic backgrounds and environmental exposures. For instance, in cancer immunotherapy, multi-omics analysis of the microbiome has revealed associations between specific microbial metabolites (eg., indolepropionic acid) and the efficacy of immune checkpoint inhibitors, though intervention outcomes may vary significantly due to heterogeneity in host immune status or intestinal niches.[72,73] Future research must validate multi-omics-guided interventions through large-scale clinical trials and develop standardized analytical workflows to support clinical translation.[74,75]

Delivery Design Strategies Targeting Oxidative Stress and Cytokine Networks

Oxidative stress and the cytokine network play key driving roles in the imbalance of the gut-brain axis and coagulation abnormalities in inflammatory bowel disease (IBD). Mitochondrial dysfunction in intestinal epithelial cells and over-activation of NADPH oxidases (eg., NOX1) can trigger a burst of reactive oxygen species (ROS), which directly disrupt tight junction proteins (eg., ZO-1, occludin) and induce epithelial cell apoptosis. Meanwhile, these events promote the polarization of macrophages toward the pro-inflammatory M1 phenotype (with an increased proportion of $CD86^+$ cells), which further secrete TNF-α, IL-6, IL-17, and IL-23, forming a positive feedback loop of "oxidative stress–inflammation–epithelial injury".[15,27,55] These cytokines not only aggravate local intestinal inflammation but also cross the blood–brain barrier via systemic circulation, activate microglia, and promote neuroinflammation, ultimately leading to extra--intestinal manifestations such as anxiety and depression.[11,62] Therefore, precise intervention targeting oxidative stress and key cytokine axes has become an important direction for multi-target therapy of IBD.

Based on integrated multi-omics analysis, patient-specific oxidative stress markers (eg., plasma 8-OHdG, lipid peroxides) and cytokine profiles (eg., IL-23/Th17 pathway activity) can be identified to guide the design of individualized delivery strategies. For instance, ROS-responsive nanocarriers (eg., polymers with thioether or oxalate backbones) encapsulating N-acetylcysteine or superoxide dismutase enable ROS-triggered drug release in the inflamed intestine, significantly reducing the side effects of systemic antioxidants.[57,72] Macrophage-targeted delivery systems, such as mannose-modified liposomes or biomimetic cell membrane nanoparticles, can precisely deliver inhibitors of the IL-6/IL-23 signaling pathway (eg., tocilizumab, risankizumab) to activated macrophages in the intestinal lamina propria. By blocking the JAK/STAT3 and RORγt pathways, these systems inhibit Th17 differentiation and downregulate the production of IL-17A and IL-22.[39,76] In addition, engineered probiotics (eg., Lactococcus lactis) can be designed to continuously secrete anti-TNF-α nanobodies or the anti-inflammatory cytokine IL-10, colonize the colonic mucosa after oral administration, and restore local immune homeostasis.[13,70] Recent studies have also shown that plant exosomes or milk-derived extracellular vesicles (eg., milk exosomes) can naturally target intestinal microfold cells (M cells), deliver miRNA-146a mimics to inhibit the macrophage TLR4/NF-κB pathway, and improve intestinal barrier function.[15,65]

These delivery strategies targeting oxidative stress and the cytokine network can not only more effectively block the local inflammatory-coagulant cascade (eg., reducing tissue factor-positive macrophages and platelet activation) but also improve systemic coagulation abnormalities and neuropsychiatric comorbidities by regulating the vagal reflex and the

gut-liver-brain axis. In the future, combined with single-cell multi-omics and spatial transcriptomics, the heterogeneity of macrophages and neutrophils at different stages of IBD can be further elucidated, providing a theoretical basis for the development of more precise cell subset-targeted delivery systems.[77,78]

AI-Driven Multi-Omics Integration Platforms

Artificial intelligence (AI) technologies provide new paradigms for deep integration and dynamic modeling of multi-omics data. Technologically, AI algorithms (eg., deep learning and graph neural networks) can extract cross-omics features from high-dimensional heterogeneous data—for example, using autoencoders for dimensionality reduction or attention mechanisms to capture key molecular modules of host-microbiota interactions.[39,76,79–82] In esophageal cancer research, AI-driven single-cell multi-omics integration revealed spatiotemporal interaction networks between microbiota and host cells in the tumor microenvironment and predicted metabolic biomarkers associated with immunotherapy response.[77,83] Additionally, AI platforms (eg., gNOMO2) support taxonomic and functional integration of microbiome multi-omics data, enabling correlation of species abundance, metabolic pathways, and host phenotypes within a unified analytical framework to significantly enhance biological interpretability.[84,85] For clinical translation, dynamic AI models (eg., recurrent neural networks) can integrate longitudinal multi-omics data to optimize personalized intervention protocols in real time.[86,87] However, the reliability of AI models depends on the development of high-quality annotated datasets and interpretable algorithms—for example, using causal inference to distinguish commensal associations from causal mechanisms[40,88–92] (Figure 3).

The promise of AI-driven multi-omics integration for precision medicine in IBD-related complications must be tempered by a realistic appraisal of its current limitations. The performance of AI models, particularly deep learning algorithms, is heavily dependent on the quality, scale, and standardization of training data.[87,90] Significant heterogeneity in data collection protocols across institutions, coupled with a lack of diverse, multi-ethnic cohorts, poses a major risk of algorithmic bias, potentially leading to models that perform well in derivation cohorts but fail in real-world, diverse patient populations.[93,94] Furthermore, the "black box" nature of many AI models limits their clinical acceptance; a prediction is less useful if the underlying biological rationale cannot be explained.[92] While tools like gNOMO2 attempt to enhance interpretability, they are still in their infancy.[84] Beyond data challenges, there is a critical "validation gap." Multi-omics signatures often identify associations, but establishing causality requires orthogonal validation in organoid models or human trials, which is frequently lacking.[95,96] For example, while the microbial metabolite TMAO is strongly associated with platelet hyperreactivity, directly proving its causative role in human IBD thrombosis and successfully targeting it without adverse effects remains a formidable challenge.[21,36] The field must, therefore, prioritize the development of standardized, shareable data ecosystems and invest in interpretable AI architectures before these tools can reliably guide clinical decisions.

Comprehensive Discussion and Future Directions

The precision intervention framework based on multi-omics is gradually transitioning from technical exploration to clinical practice, but its full application still faces multiple challenges. First, data integration bottlenecks restrict the deep analysis of cross-omics data: data generated by single-cell omics and spatial omics technologies exhibit significant temporal-spatial heterogeneity, requiring the development of novel standardized tools (such as the Multi-omics Integration Iterative Tracking framework/MIIT) to achieve dynamic alignment and functional correlation analysis of cross-scale data.[97,98] Second, insufficient causal validation limits the clinical translation value of multi-omics discoveries. For example, the interaction mechanism between host genes and gut microbiota needs to be jointly validated through in vitro organoid models and animal experiments to clarify whether specific microbial metabolites (such as secondary bile acids) directly regulate coagulation factor expression or platelet function.[37,95,96,99–102] Additionally, the problem of clinical applicability urgently needs to be solved: the reproducibility and universality of existing multi-omics-guided intervention strategies in real-world settings are limited. It is necessary to establish a global multi-center collaboration network, unify data collection standards, and include diverse population cohorts to overcome the interference of racial, geographical, and environmental factors on research conclusions.[93,94,103–106]

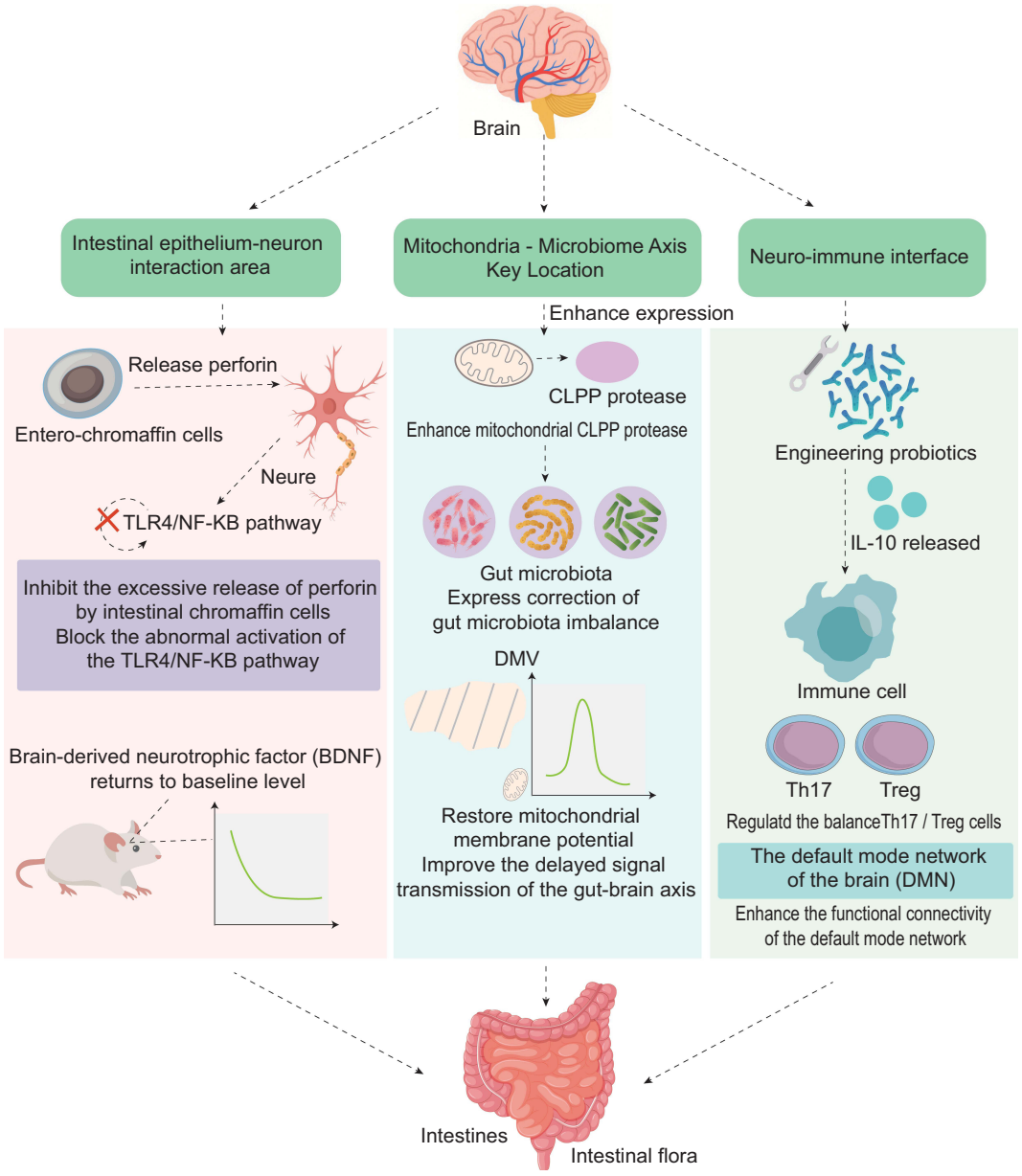

Figure 3 Mechanism of Intervention at Key Nodes Based on the Gut-Brain Axis. This figure outlines emerging multi-target therapeutic strategies designed to disrupt the pathological "inflammation-neuro-coagulation" network by modulating specific GBA nodes. Modulating Intestinal Epithelial-Neural Crosstalk: Inhibiting excessive perforin release from enterochromaffin cells blocks the aberrant activation of the neuronal TLR4/NF-κB pathway. This intervention successfully restores physiological levels of brain-derived neurotrophic factor (BDNF) in pre-clinical colitis models, highlighting a direct link between intestinal immune activation and neuronal health. Targeting the Mitochondria-Microbiota Axis: Enhancing mitochondrial caseinolytic protease P (ClpP) expression in neurons of the dorsal motor nucleus of the vagus (DMV) restores mitochondrial membrane potential (ΔΨm). This ameliorates intestinal dysbiosis and corrects delayed signal transmission along the GBA, improving gut motility and barrier function. Re-engineering the Neuroimmune Interface with Combinatorial Therapy: A synergistic approach combines transcutaneous magnetic stimulation (TMS) with orally administered engineered probiotics (e.g., Lactococcus lactis secreting IL-10). TMS modulates central neural circuits, while probiotics colonize the colonic mucosa to restore local immune homeostasis. This dual modulation effectively restores the peripheral Th17/Treg balance and, as assessed by resting-state functional MRI (rs-fMRI), enhances functional connectivity within the brain's default mode network (DMN), offering a unified strategy to treat both intestinal and neuropsychiatric manifestations.

Future research needs to deeply integrate cutting-edge technologies with clinical needs. With breakthroughs in single-cell spatial multi-omics technologies, high-resolution analysis of cross-organ interaction networks in the intestinal microenvironment and extra-intestinal organs (such as the liver and brain) of IBD patients will be achievable. Combined with artificial intelligence (AI) algorithms (such as deep spatio-temporal modeling), it will be possible to predict the dynamic evolution laws of the coagulation-inflammation-microbiota network and formulate personalized intervention thresholds.[41,78,107–111] Ultimately, this framework will drive the transformation of the medical paradigm from "disease treatment" to "health

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maintenance," achieving full-cycle management of IBD-related coagulation dysfunction and extra-intestinal manifestations through early risk warning and targeted regulation.

Challenges and Future Directions

Despite ongoing advances in research on coagulation dysfunction associated with IBD, mechanistic exploration and clinical translation still face numerous challenges. First, at the mechanistic research level, key scientific questions remain incompletely clarified. For example, whether gut-brain axis signals (such as vagus nerve stimulation) directly regulate the synthesis of hepatic coagulation factors (eg., fibrinogen, prothrombin) still lacks direct experimental evidence, limiting the development of therapeutic strategies targeting neuro-coagulation pathways.[33,34,112–116] Meanwhile, the single-cell omics characterization of platelet functional heterogeneity is insufficient, making it difficult to clarify the specific roles of certain platelet subsets (eg., pro-inflammatory or anticoagulant types) in IBD-related thrombosis or bleeding. Spatial transcriptomics technologies are needed to achieve precise localization.[117,118]

Second, clinical translation bottlenecks urgently need to be addressed. On one hand, standardized integration of multi-omics data (eg., gut microbiota metagenomics, coagulation proteomics) faces technical challenges, and the long-term safety of microbial transplantation (eg., fecal microbiota transplantation) raises ethical controversies, requiring the establishment of interdisciplinary ethical review frameworks.[38,119,120] On the other hand, significant racial or regional differences in the cut-off values of existing biomarkers (eg., D-dimer, NETs-associated proteins) may lead to biases in anticoagulation treatment decisions, necessitating validation of their universality through global multicenter studies.

Future research should focus on the following directions: decoding the regulatory network of the gut-brain-liver axis on coagulation balance through organoid models and gene editing technologies; using single-cell multi-omics technologies to reveal the dynamic evolution of platelet heterogeneity in extra-intestinal thrombus formation in IBD; developing multi-omics analysis platforms that balance data standardization and ethical norms; and establishing thrombus risk stratification models based on racial/regional characteristics to ultimately promote the clinical translation of personalized coagulation management strategies.

Ultimately, the central challenge in translating these promising directions into clinical reality is not merely technological, but conceptual. The field must shift from a reductionist pursuit of single "master regulators" (like a specific cytokine or bacterial strain) towards a holistic understanding of the dynamic, adaptive networks governing the "inflammation-neuro-coagulation" triad.[18,38] This requires abandoning static disease classifications in favor of dynamic, multi-scale models that can account for feedback loops and system resilience. Furthermore, the ethical and regulatory frameworks for therapies targeting the microbiome and gut-brain axis are nascent and ill-defined.[119,120] For instance, the long-term ecological consequences of fecal microbiota transplantation or engineered probiotics on an individual's microbiome are largely unknown. Similarly, modulating neural pathways like the vagus nerve carries inherent risks of off-target effects on other organ systems. Therefore, progress in this field will depend as much on the development of robust ethical guidelines and innovative clinical trial designs that can capture complex, system-level outcomes as it will on technological breakthroughs in omics and AI.

The conceptual framework of the "inflammation-neuro-coagulation" triad, while providing a unifying model for the systemic pathologies of IBD, also illuminates the inherent limitations of reductionist approaches. This triad should not be viewed as three separate, linearly connected pathways, but as a single, highly dynamic and adaptive network where each node continuously modulates the others through complex feedback loops.[18,38] For instance, while we have discussed how gut-derived IL-6 can promote neuroinflammation and a pro-coagulant state, emerging evidence suggests that the resultant microglial activation can, in turn, signal back to the gut via neural pathways, potentially exacerbating intestinal inflammation and barrier dysfunction.[15,62] Similarly, the pro-thrombotic state, characterized by platelet activation and fibrin deposition, is not merely an endpoint of inflammation but actively shapes the immune microenvironment. Activated platelets can directly modulate the function of dendritic cells and T-cells, potentially skewing the immune response towards a Th17 phenotype, which is central to IBD pathogenesis.[25,117] Therefore, future research must move beyond identifying individual associations within this triad and towards understanding its emergent properties. This requires the application of systems biology approaches that can model these dynamic, non-linear interactions, integrating data from multi-omics platforms to predict how perturbations at one node (eg., stress-induced HPA axis activation) will reverberate throughout the entire network, ultimately determining the clinical trajectory from local intestinal inflammation to systemic extra-intestinal manifestations.[30,108]

Conclusion and Prospects

Study identification and selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. From an initial pool of 512 records sourced from databases, 100 records were removed prior to screening (88 duplicates and 12 flagged by automation tools). The titles and abstracts of the remaining 412 records were screened, which led to the exclusion of 232 irrelevant publications. We subsequently retrieved 180 full-text articles for detailed eligibility assessment; 15 of these were unavailable, leaving 165 articles for full-text review. During this stage, 45 articles were excluded for the following reasons: irrelevant population or intervention (n=18), non-English language (n=7), publication type such as review or commentary (n=10), and insufficient data (n=10). This rigorous process culminated in the inclusion of 120 studies for the final systematic review and data synthesis (Figure 4).

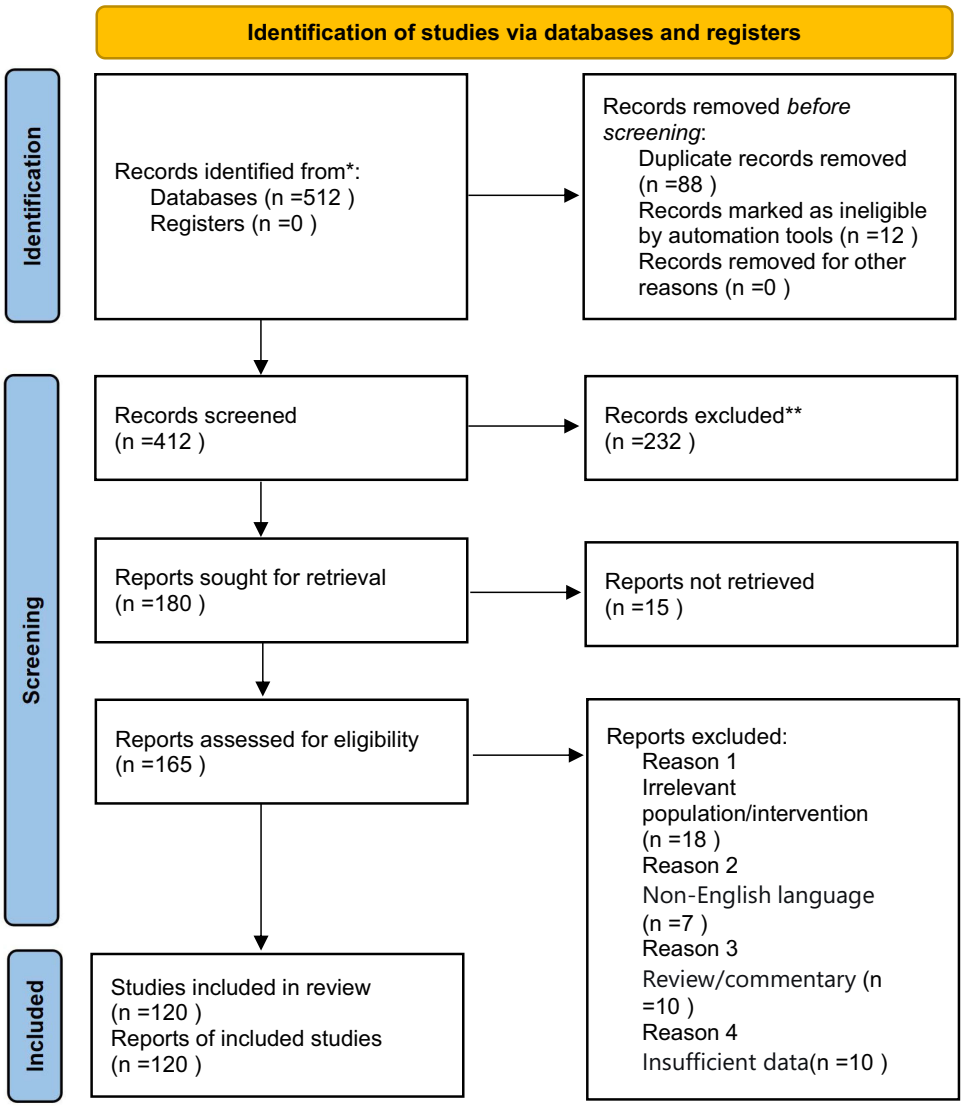

Figure 4 PRISMA 2020 Flow Diagram for Systematic Reviews. The systematic review and data synthesis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A total of 512 records were initially identified from database searches. After the removal of 88 duplicate records and 12 records marked as ineligible by automation tools, 412 records were screened based on titles and abstracts, leading to the exclusion of 232 irrelevant publications. Full-text articles were sought for the remaining 180 reports, of which 15 could not be retrieved. The remaining 165 full-text articles were assessed for eligibility. Of these, 45 were excluded for the following reasons: irrelevant population or intervention (n=18), non-English language (n=7), publication type (e.g., review, commentary) (n=10), and insufficient data (n=10). Consequently, 120 studies were included in the final systematic review and data synthesis. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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This review synthesizes current evidence to establish the gut-brain axis (GBA) dysregulation as a central pathological driver in inflammatory bowel disease (IBD), orchestrating a complex interplay of inflammation, neuro-immune signals, and coagulation dysfunction—a concept we define as the "inflammation-neuro-coagulation" triad. Unlike traditional models that view intestinal inflammation, neuropsychiatric symptoms, and thromboembolic events as separate entities, this triad framework reveals their interconnected nature, explaining the high prevalence of extra-intestinal manifestations in IBD patients. Our analysis leads to several principal conclusions that redefine our understanding of IBD pathophysiology and its clinical management.

First, the GBA serves as a critical conduit for the systemic propagation of IBD pathology. We have detailed how gut-derived inflammatory cytokines (IL-6, TNF-α) and microbial metabolites (eg., TMAO, SCFAs) not only perpetuate local intestinal damage but also directly access the central nervous system (CNS) via the blood-brain barrier, triggering neuroinflammation and altering CNS function. Conversely, chronic stress activates the HPA axis and vagal pathways, creating a bidirectional feedback loop that exacerbates both intestinal inflammation and systemic coagulopathy. The liver emerges as a crucial hub in this axis, integrating gut-derived signals to modulate the hepatic synthesis of coagulation factors, thereby directly linking intestinal health to systemic thrombotic risk. This gut-brain-liver perspective is essential for understanding the dynamic nature of coagulation balance in IBD.

Second, coagulation abnormalities in IBD are not merely a downstream consequence of inflammation but an active and integral component of the disease network. We have highlighted how the "leaky gut" triggers systemic inflammation (via TLR4/MyD88 signaling), leading to endothelial tissue factor (TF) upregulation and activation of the extrinsic coagulation cascade. This is compounded by a unique genetic and metabolic profile in IBD patients, including reduced PROCR expression and an increased prevalence of Factor V Leiden mutations. Microbial metabolites, particularly TMAO, directly prime platelet hyperreactivity. The resulting state is highly dynamic, with patients paradoxically at risk for both bleeding (due to malnutrition and vitamin K deficiency) and thrombosis, a clinical challenge that requires nuanced, personalized management.

Third, the complexity of the "inflammation-neuro-coagulation" network necessitates a paradigm shift from reductionist approaches to multi-omics-driven precision medicine. Static biomarkers and conventional staging systems are inadequate to capture the dynamic evolution of this multidimensional network. Our review strongly advocates for the integration of metagenomics, metabolomics, and single-cell transcriptomics to build dynamic models. Such models can monitor the interplay between the microbiome, host metabolism, and coagulation markers, enabling precise assessment of disease activity and individualized prediction of thrombotic or bleeding risks. This approach is foundational for moving beyond "one-size-fits-all" anticoagulation strategies.

Finally, targeted interventions at key GBA nodes offer unprecedented therapeutic opportunities. We have discussed promising preclinical and early-stage strategies, including the elimination of TF^+ T cells, modulation of vagal nerve activity via taVNS, and the use of engineered probiotics to deliver anti-inflammatory molecules. These approaches aim to break the inflammation-coagulation vicious cycle at its source. Looking forward, the development of AI-assisted clinical decision support systems that integrate real-time biomarker data (eg., from novel non-invasive sensors) with multi-omics predictions represents a transformative paradigm. Such systems could provide clinicians with dynamic risk assessments, guiding the optimal timing and intensity of both anti-inflammatory and anticoagulant therapies.

To bridge the gap between current knowledge and clinical application, a phased roadmap with realistic timeframes is essential. In the short term (2–3 years), efforts should concentrate on validating multi-omics-derived biomarker panels—such as integrated metagenomic, metabolomic, and coagulation markers—in large, prospective multicenter cohorts to refine risk stratification for thromboembolic events in IBD patients.[24,65] Concurrently, early-phase clinical trials of targeted interventions, including engineered probiotics[53] and non-invasive neuromodulation techniques,[36] are expected to provide initial proof-of-concept efficacy and safety data. In the medium term (5–7 years), we anticipate the development and validation of AI-powered clinical decision support systems that integrate real-time biomarker monitoring with multi-omics profiles to personalize anticoagulation therapy, potentially reducing both thrombotic and bleeding complications.[72,108] Furthermore, advances in single-cell and spatial omics technologies will likely elucidate the functional heterogeneity of platelets and their interactions with the gut-brain-liver axis, paving the way for cell-specific therapies.[67,101] In the long term (beyond 10 years), a comprehensive understanding of the dynamic inflammation-neuro-coagulation network, coupled with robust ethically compliant data-sharing platforms, could enable preemptive modulation of disease trajectories, shifting the paradigm from

treatment to prevention.[30,38] Achieving these milestones will require sustained multidisciplinary collaboration and iterative feedback between mechanistic studies and clinical trials. Through multidisciplinary collaboration and technological innovation, it is expected to break through existing therapeutic bottlenecks and improve the long-term prognosis and quality of life for IBD patients.

In conclusion, future research must prioritize the translation of these conceptual frameworks into clinical practice. Key challenges to be addressed include: (1) elucidating the precise regulatory circuits of the gut-brain-liver axis on coagulation factor synthesis using organoid models and gene-editing technologies; (2) characterizing the functional heterogeneity of platelets in IBD using spatial transcriptomics to identify novel therapeutic targets; and (3) establishing robust, ethically compliant, and globally representative multi-omics data-sharing platforms to develop racially stratified risk models. By embracing a holistic, systems biology perspective, we can overcome the current therapeutic bottlenecks and significantly improve the long-term prognosis and quality of life for IBD patients burdened by coagulation disorders and extra-intestinal manifestations.

Data Sharing Statement

All data included in this review article are derived from previously published studies and are freely available in the respective databases or journals. No additional raw data were generated for this review.

Ethical Approval

This review article did not involve any animal or human testing, and no ethical approval was required. All authors confirm that the manuscript adheres to standard ethical guidelines for publication, and all study procedures were carried out in accordance with relevant ethical standards. The authors also declare that there were no ethical concerns related to the data sources used in this review.

Informed Consent

Not applicable. As this is a review article and did not involve any human participants or personal data collection, no informed consent was required from individuals.

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Author Contributions

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

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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