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REVIEW

Intestinal barrier in chronic gut and liver diseases: Pathogenesis and therapeutic targets

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Abstract The intestinal barrier is the primary defense that separates the host from the external environment, possessing several crucial physiological functions, including nutrient digestion, absorption, and protection against potentially harmful dietary antigens and pathogenic microorganisms. Nevertheless, various factors, such as diet, medications, circadian rhythm disturbances, gut microbiota, microbial metabolites, and genetic predisposition, can disrupt the intestinal barrier. Such disruption may lead to bacterial translocation, subsequently triggering enterohepatic and systemic inflammation. Impaired intestinal barrier has been implicated in the pathogenesis of numerous diseases, particularly chronic gut and liver diseases. In this review, we will summarize the fundamental functions of intestinal barrier and discuss clinical correlations between intestinal barrier dysfunction and diseases such as colitis, colorectal cancer, and chronic liver diseases including metabolic dysfunction-associated steatohepatitis, alcohol-associated liver disease, and primary sclerosing cholangitis. Additionally, we will also highlight some potential therapeutic strategies aimed at restoring barrier integrity to improve disease management.

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1. Introduction

The preservation of barrier integrity is a crucial indicator of health and is essential for withstanding environmental stress while supporting physiological functions[1−5]. This internal biological barrier facilitates the establishment of ventricular electrophysiological and chemical gradients, osmotic equilibrium, coordination of ventricular communication, and normal turnover of metabolic circuits. Meanwhile, the external barrier, primarily represented by the intestinal cavity, serves as a "boundary line" that prevents the translocation of harmful substances and microorganisms from the gut into the systemic circulation[6,7]. The intestinal barrier is a complex structure and comprises several components: mucus layer, epithelial tight junctions (TJs) and adherens junctions (AJs), stem cell niches, mesenchymal cells, resident immune cell population, and symbiotic gut microbiota[8−16]. The physical barrier is formed by a dense epithelial layer, composed of specialized cells originating from crypt stem cells, including enterocytes, goblet cells, Paneth cells, tuft cells, M cells, and other enteroendocrine cells[17−21]. These cells are interconnected by TJs that regulate intestinal homeostasis, working in conjunction with biochemical barriers constructed by self-secreting host factors and microbial metabolites.

Over the past few decades, many clinical disorders have been associated with intestinal barrier dysfunction[22−24]. These conditions include intestinal diseases, such as inflammatory bowel disease (IBD), which is comprised of ulcerative colitis (UC) and Crohn's disease (CD), as well as irritable bowel syndrome (IBS) and colorectal cancer (CRC). Beyond the gut, chronic liver diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), alcoholic liver disease (ALD), and primary sclerosing cholangitis (PSC), and systemic metabolic disorders such as diabetes and obesity, are also linked to impaired intestinal barrier integrity. However, most clinical data remains correlational, leaving unresolved whether intestinal barrier damage is a cause or a consequence of these diseases[25]. Currently, no US Food and Drug Administration (FDA)-approved medications are specifically designed to repair intestinal barrier damage. Most therapies focus on the prevention and management of the related diseases, often relying heavily on immunosuppressants to control inflammation[26,27]. Unfortunately, persistent barrier impairment and delayed healing can reduce the efficacy of these treatments, and potentially lead to treatment tolerance and even relapse[28]. Therefore, it is essential to develop therapeutic strategies that directly target the epithelial barrier. Further research is necessary to better understand the physiological regulation of the intestinal barrier, the mechanisms underlying its dysfunction, and its role in disease development and progression.

This review discusses the physiological structure and function of the intestinal epithelial barrier, the internal and external factors affecting its integrity, and the role of barrier impairment in disease pathogenesis. We aim to provide insights that may guide future research on developing therapies targeting the intestinal barrier dysfunction and related diseases.

2. Structural composition of intestinal barrier

The intestine is a unique organ with crucial roles in food digestion, nutrient absorption, dynamic host-environment interaction, and body homeostasis maintenance. To protect the host from external threats, such as prolonged exposure to dietary antigens and pathogenic microorganisms, intestinal epithelial cells (IECs) form multiple types of barriers, including a mechanical barrier, a mucus layer enriched with symbiotic microbes, and an immune barrier composed of immune cells and their active substances (Fig. 1). The mechanical barrier consists of a compact layer of IECs formed by TJs, which ensure the structural integrity of the intestine, regulate intestinal permeability, and control the transportation of water and macromolecules[29]. The mucus layer, made of mucin secreted by goblet cells, provides both habitat and nutrients for symbiotic bacteria. Its unique structural characteristics restrict the penetration of pathogens, further enhancing the physical isolation function of TJs[30]. Furthermore, there is a stem cell niche located at the base of the crypt, which consists of crypt-resident intestinal stem cells (ISCs), mesenchymal cells, immune cells, and intestinal secretory cells, such as goblet and Paneth cells. This niche is highly proliferative and thus is responsible for tissue renewal and intestinal barrier repair. It also mediates antigen phagocytosis and releases antimicrobial peptides (AMPs) to maintain internal homeostasis by eliminating potential pathogens[31]. Together, these elements create physical and biochemical barriers that protect the host and regulate communication between the internal and external environments. This intricate balance is essential for the proper functioning of the gastrointestinal system and the maintenance of overall bodily equilibrium.

2.1. *Mucus layer composition and immune surveillance*

The mucus layer serves as the first line of defense for the gastrointestinal tract, primarily consisting of 90%−95% water, 1%−2% lipids, and 1%−5% mucins. The mucins are highly glycosylated with 50%−80% carbohydrates (*w*/*w*) by glycosyltransferases. The diverse and complex structure of glycans in mucin provides colonization sites and nutrients to the mucus-associated bacteria that inhabit the mucus niche[32]. Mucin 2 (MUC2), the main mucin expressed in the gastrointestinal tract, is secreted by goblet cells upon bacterial exposure *via* meprin β-mediated cleavage, forming a protective mucin layer[33]. The structure of the mucus layer allow symbiotic microbiota to colonize in the outer mucus layer and utilize their polysaccharide-degrading enzymes to derive nutritional energy from mucin *O*-glycan[9,34,35]. This interaction helps regulate the structure and transcription of the proximal colon microbiota[36]. A low-fiber diet has been shown to promote degradation of host mucins by the microbiota, leading to a thinner mucus layer and, consequently, a weakened barrier[37]. *Muc2*-deficient mice displayed increased colon histological damage, greater bacterial translocation to the liver, and a marked reduction in intestinal TJ proteins[38]. Furthermore, impairment of mucus barrier integrity and function due to mucin *O*-glycosylation disorders has been implicated in the

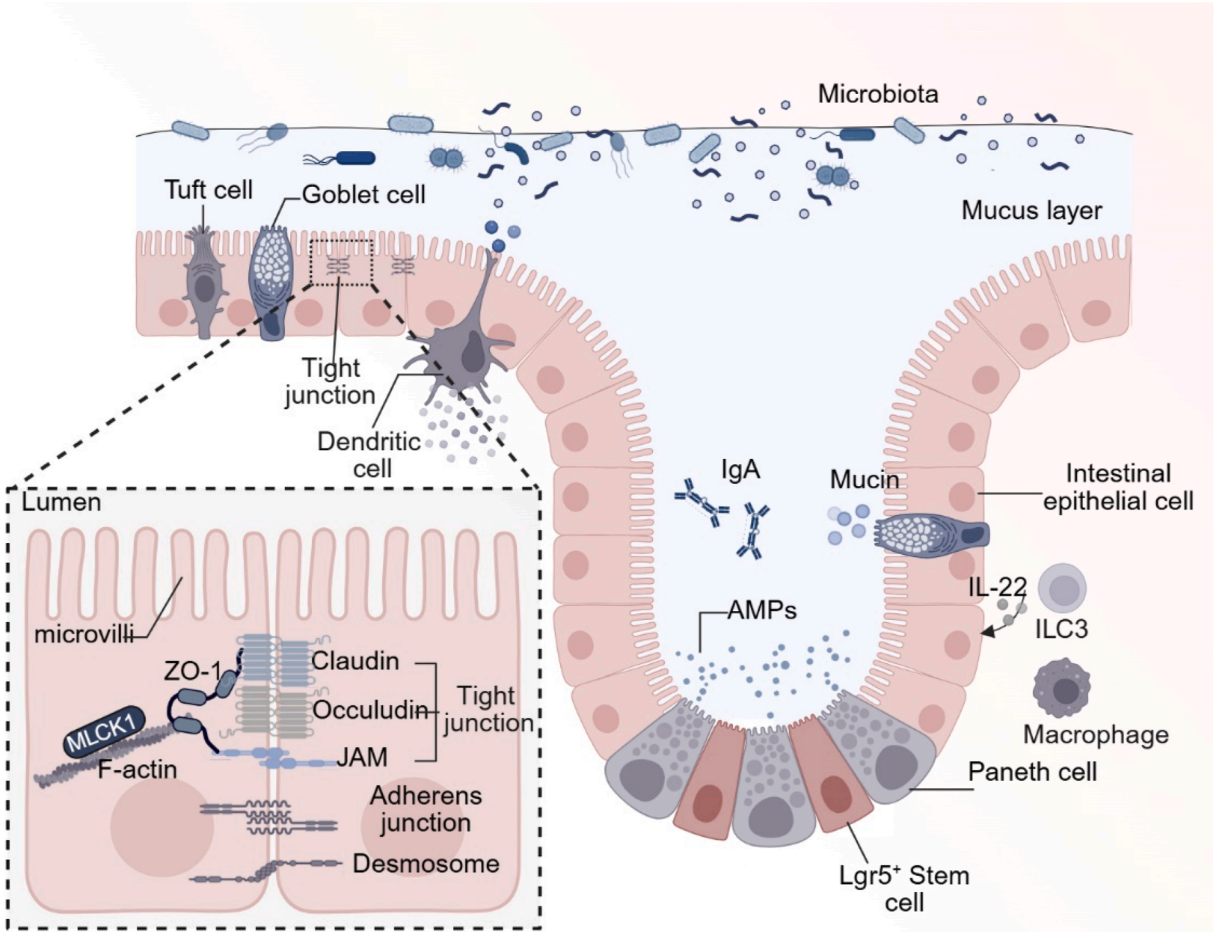

Figure 1 Structural composition of the intestinal barrier. The intestinal barrier is the largest barrier separating the host from the external environment, and has the physiological function of protecting the host from continuous antigen exposure to and invasion by pathogenic microorganisms. Maintaining the integrity of the intestinal barrier is important for overall health. The intestinal barrier comprises the mucus layer barrier, the mechanical barrier, the stem cell niche formed by intestinal stem cells and differentiated specialized cells, and the immune barrier. The mucus layer provides a habitat and nutrient components for the symbiotic microbiota, while limiting the penetration of pathogens due to its unique structural characteristics. The dense layer of epithelial cells formed by tight junctions determines the structural integrity of the intestine and intestinal permeability, which controls the transport of water and macromolecules. Crypt-resident stem cells maintain the continuous regeneration and damage repair of the intestinal epithelium, and mediate differentiation into different types of intestinal cells to support the functional diversity of the intestinal epithelium. The intestinal epithelial barrier is essential for preserving the integrity, function, and homeostasis of the intestinal structure. ZO-1, zonula occludens 1; MLCK, myosin light chain kinase; JAM, junctional adhesion molecule; MUC, mucin; AMP, antimicrobial peptides. Created with Biorender.com.

pathogenesis of metabolic diseases[39]. Recent studies have identified Gasdermin D (GSDMD), a pore-forming effector protein involved in pyroptosis, regulates mucin secretion in goblet cells by promoting calcium-dependent exocytosis *via* scinderin-mediated F-actin depolymerization. GSDMD deficiency disrupts the mucus barrier, enabling pathogen adhesion to the epithelium and leading to the intestinal disease pathogenesis[40].

The viscosity of mucus also supports the retention and diffusion of antibacterial substances from Paneth cells and goblet cells, and immune-derived cytokines, which collectively protect the host from infection[32]. AMPs, such as crypt defensins, antimicrobials, and lysozymes, are produced by Paneth cells. These APMs are abundantly on the surface of intestinal epithelium and capable of eliminating harmful microorganisms directly. In neonatal non-obese diabetic mouse models, colonic AMP deficiency due to ecological dysregulation contributes to pancreatic aotoimmunity in type 1 diabetes[41]. AMPs, along with microbe-specific immunoglobulin IgA, play a crucial role in maintaining barrier stability and inhibiting inflammation[42]. Their regulation is influenced by IL-17 and IL-22, which are produced by T helper 17 (Th17) cells and type III innate lymphoid cells (ILC3)[43]. The latter relies on the dendritic cell (DC)-associated Mincle signaling pathway, which is linked to the tyrosine kinase-coupled C-type lectin receptor. In the absence of Mincle or when tyrosine kinase is impaired, the synthesis of intestinal regenerating islet-derived III-γ (RegIIIγ) and IgA is reduced, permitting gut microbiota translocation that drives hepatic inflammation and lipid metabolism dysregulation[43]. These findings demonstrate the crucial role of mucus layer integrity in maintaining gut−liver homeostasis.

2.2. *Composition of epithelial junctions*

Microvilli, apical projections of IECs, expand the intestinal surface area, optimizing nutrient contact with specific receptors and

digestive enzymes expression to enhance intestinal absorptive function[44]. The densely packed microvilli form the brush border, a barrier that also prevents bacterial attachment to IECs. In patients with CD, studies revealed transcriptional dysregulation in genes associated with the brush border and reduced microvilli length, suggesting a possible link between microvillus abnormalities and epithelial lesions[45]. The microvilli-stabilizing actin ACT-5, forming a bundle structure that maintains the normal morphology of intestinal microvilli, is disrupted by virulence factors of enterohemorrhagic *Escherichia coli via* CDK1-Formin signaling axis, leading to microvilli effacement, IEC barrier dysfunction, and worsens diseases such as severe diarrhea and hemorrhagic colitis[46].

The apical junction complex consists of TJs, AJs, and desmosomes. Under physiological conditions, TJs localize near the plasma membrane between adjacent cells, where anastomosis chains merge neighboring cell membranes and seal the paracellular space[29,47]. One of the key roles of TJs is to form an epithelial permeability barrier that selectively regulates solute transport and charge flux, providing an essential "gate and fence" function[48]. The claudin protein family, which has a four-transmembrane domain structure, is integral to TJ formation. Claudins determine the charge selectivity of the paracellular channel and are essential for proper TJ function[49]. Generally, the downregulation of claudins promotes the progression of inflammatory and metabolic disorders due to barrier and paracellular channel defects. Conversely, elevated claudin-2 levels accelerate the onset of IBD, as claudin-2 acts as a pore barrier to increase intestinal cationic permeability, fostering inflammatory responses[50].

Zonula occludens 1 (ZO-1), the first discovered TJ protein, serves as a scaffold that positions several transmembrane proteins, such as occludin, claudin, and junctional adhesion molecule (JAM), at the cell−cell junctions to strengthen the bond between TJs and the actin cytoskeleton[29,51]. ZO-1 anchors the TJ cytoskeleton, maintaining structural integrity and serving as a key barrier function marker. While essential for TJ stability, its direct role in TJ assembly and signaling remains undefined. Reduced ZO-1 expression in IBD might result from abnormal orientation of the mitotic spindle due to disrupted Wnt-β-catenin signaling, which inhibits epithelial proliferation and mucosal repair rather than impaired TJ-dependent barrier function[52].

TJs are central to barrier regulation, and their breakdown can be a primary pathophysiological factor in pathogen invasion. Loss of TJs compromises the barrier and is associated with aberrant adenosine cAMP/protein kinase A (PKA)−cAMP response element-binding protein (CREB) signaling pathway[53]. Additionally, the cytoskeleton critically regulates TJ dynamics and epithelial integrity. The pathogen *Chlamydia trachomatis* utilizes the effector protein *TepP* to disrupt host cytoskeleton-regulated tyrosine phosphorylation during the initial phase of infection, leading to TJ disassembly and further infection[54]. TRIM40, an E3 ubiquitin ligase, disrupts epithelial barrier integrity by targeting ROCK1, a critical kinase for cell−cell junction integrity, destabilizing cortical actin and promoting IBD pathogenesis[55].

2.3. *Stem cell niche and specialized epithelial cells*

The continuous proliferative capacity of the intestinal crypt supports the maintenance and renewal of intestinal barrier. ISCs, located at the base of the crypt, plays a key role in both tissue repair and self-renewal to resist hazards within the digestive tract by continually replenishing damaged IECs[56]. In response to pathogen infection or epithelial injury, elevated IL-1R1 signaling induces the production of RSPO3, a Wnt agonist that promotes self-renewal of ISCs and facilitates IL-22-driven barrier repair[57]. Intestinal barrier damage is often attributed to the dysfunction of stem cell niche, and several studies have demonstrated the environment factors, psychological stress, and aging are able to impair ISC lineage commitment. ISCs differentiate into diverse secretory and absorptive enterocytes in response to microenvironmental signals and nutrient availability[56]. Psychological stress modifies sympathetic nerve output, which affects ISC mitochondrial bioenergetics *via* microbial metabolites and thus influences ISC differentiation and epithelial barrier repair. This mechanism partially explains the increased vulnerability to intestinal diseases in patients with mental disorders[58]. Similarly, aging compromises barrier integrity *via* ISC depletion and dysbiosis, resulting from diminished Wnt signaling produced by Paneth and mesenchymal niche cells essential for ISC maintenance[59].

In addition to Paneth cells and goblet cells, tuft cells represent another specialized secretory IEC type within the epithelial barrier. Tuft cells play a protective role against pathogen infections by secreting the cytokine IL-25, which activates lamina propria lymphocytes to drive type 2 immunity and pathogen clearance[60]. Tuft cells interact with pathogen metabolites *via* membrane receptors like Vmn2r26, initiating G-protein-coupled signaling to produce prostaglandin D2 (PGD2). This stimulates goblet cell mucus secretion and SpiB-mediated tuft cell proliferation, amplifying antimicrobial defense[61]. Furthermore, tuft cells can function as reserve ISCs during intestinal injury to aid the barrier repair[62].

3. Factors in the regulation of intestinal epithelial barrier

The integrity of the intestinal barrier is affected by a variety of intrinsic and extrinsic factors. Barrier dysfunction can be triggered by genetic susceptibility, the preference for a western diet, the use of antibiotics and drugs, disruptions in circadian rhythms, psychological stress, and aging (Table 1)[37,64−70,72,73,89,95−97,99,106,108,113,118,133,134,136−138,140,146−148,151−153,209]. These influences often lead to imbalances in gut microbiota, which can induce systemic metabolic disorders (Fig. 2). The subsequent inflammation due to these metabolic disturbances further weakens intestinal barrier, and thus establishes a damaging cycle of ongoing deterioration.

3.1. *Genetic susceptibility*

Advancements in genome-wide association studies (GWAS) have notably enhanced the identification of disease-susceptibility genes and the understanding of associated biological pathways, which are valuable for clinical translation. These studies analyze genetic variants in genome to explore the relationships between genotype and phenotype[63]. While direct links between genetic mutations and intestinal barrier dysfunction are limited, GWAS has identified numerous loci associated with IBD development[64,65]. For instance, the *IL10* gene mutation was one of the first mutations found to induce IBD[66]. *Il10* knockout mice spontaneously develop colitis and increase intestinal microbiota translocation. Mutations in the IL10 receptor (IL10R), composed of IL10R1 and IL10R2 proteins encoded by *IL10RA* and *IL10RB* genes, have been associated with early-onset enterocolitis. These mutations impair IL10-induced signaling, that potentially increases the secretion of

Table 1 Factors and mechanisms of gut and liver diseases linked to intestinal barrier dysfunction.

Class	Type of disease	Affecting factors	Potential mechanism
Gut disease	UC and CD	Genetic predisposition[64–68,70,137]	Defects in genes and pathways associated with innate and adaptive immunity, autophagy, and mesenchymal cells may mediate CD susceptibility [64]. Mutations in IL10R induce hyperinflammatory immune responses in the intestine[66]. Defect in *SLC26A3*, a novel susceptibility gene for IBD, causes abnormal expression of TJ and AJ through a post-transcriptional mechanism[69]. *ST6GALNAC1* (*ST6*) mutation leads to abnormal mucin glycosylation modification, which causes dysbiosis and inflammatory activation by impairing the integrity and function of the intestinal mucus barrier[70]. Impaired cellular adhesion regulation during intestinal wound repair and disease development[136].
		BA dysregulation[72,73]	Cholic acid impede *Lgr5*$^{+}$ ISC proliferation by suppressing PPARα, ultimately impairing epithelial barrier regeneration[72]. TGR5-mediated BA signaling in ISCs activates SRC/YAP-dependent transcriptional programs driving epithelial renewal[73].
		Dysbiosis[96]	Depletion of SCFA-producing microbiota leads to barrier dysfunction *via* suppressing TJ related protein expression and mucus production[96,97].
		Circadian rhythms[99]	Disruption of this diurnally regulated diet increases the burden of exposure to dietary antigens and microbial stimuli through the disruption of microbiome-MHC II-IL-10 epithelial barrier axis, driving Crohn-like enteritis[99].
		Drug usage[89,118]	Antibiotics disrupted mucin secretion, enabling microbiota penetration and translocation into circulation, thereby causing intestinal inflammation[113]. Anti- PD-1 immunotherapy reduces IL-22 production by LTi cells, thereby exacerbating intestinal inflammation[118].
		Diet[37,106]	Transient HFD exacerbates colitis through elevating intestinal BAs and TNF levels, which together trigger cytotoxic BA accumulation in the endoplasmic reticulum, ultimately inducing intestinal epithelial apoptosis *via* the IRE1α/XBP1 pathway[106]. Fiber-deficient diets shift microbial metabolism toward mucin degradation, compromising the mucus barrier and creating an ecological niche for pathobiont expansion[37].
		Mucosal immune activation	TNF-α signaling activates the MLCK promoter, increasing long-chain MLCK expression[133] IL-13 affects epithelial barrier permeability by increasing the expression of cladin-2, and causes epithelial cell apoptosis and barrier resitution velocity[134]
	IBS	Genetic predisposition[138]	
	CRC	Dysbiosis[95]	FFAR2-mediated microbial metabolite sensing orchestrates protective effects on epithelial integrity, microbial ecology, and immune surveillance within the tumor microenvironment[95].
		Diet[108]	HFD-induced colorectal carcinogenesis involves synergistic effects of gut dysbiosis, microbial metabolite LPA-mediated CRC cell proliferation and impair cell junction, and compromised epithelial barrier function[108].
		Genetic predisposition[140]	Early genetic events disrupt intestinal barrier-related ptotein and results in microbial product infiltration into adenomatous tissue, triggering IL-23/IL-17-mediated tumour growth[140].
Chronic liver diseases	MASLD	Dysbiosis[146]	MASH patient fecal EVs drive gut−liver axis dysfunction through concurrent TJ suppression, TLR4/LPS-mediated inflammation, and HSCs activation[147].
		Alcohol exposure	ALDH2 deficiency exacerbates alcohol-induced oxidative stress, intestinal epithelial apoptosis, and TJ/AJ degradation, thereby increasing gut permeability and endotoxemia to drive systemic inflammation and liver injury[148].
	ALD	Alcohol exposure	Alcohol depletes intestinal cDCs, impairing IL-12/IFN-γ-mediated AMP production and reducing *A. muciniphila* abundance[209].
		Dysbiosis[151]	*Klebsiella pneumoniae* destroys the epithelial barrier, initiates bacterial translocation and the Th17 immune response in the liver, and increases the susceptibility to hepatobiliary injury[151].
	PSC	Dysbiosis[151]	LPS-mediated hepatocellular NF-κB activation protects cholestatic liver injury through negative feedback by inhibiting BA metabolism[153].
		ISCs stemness impairment	BDL-induced cholestatic injury involves the activation of ER stress and disruption of ISCs stemness that exacerbate systemic inflammation[152].

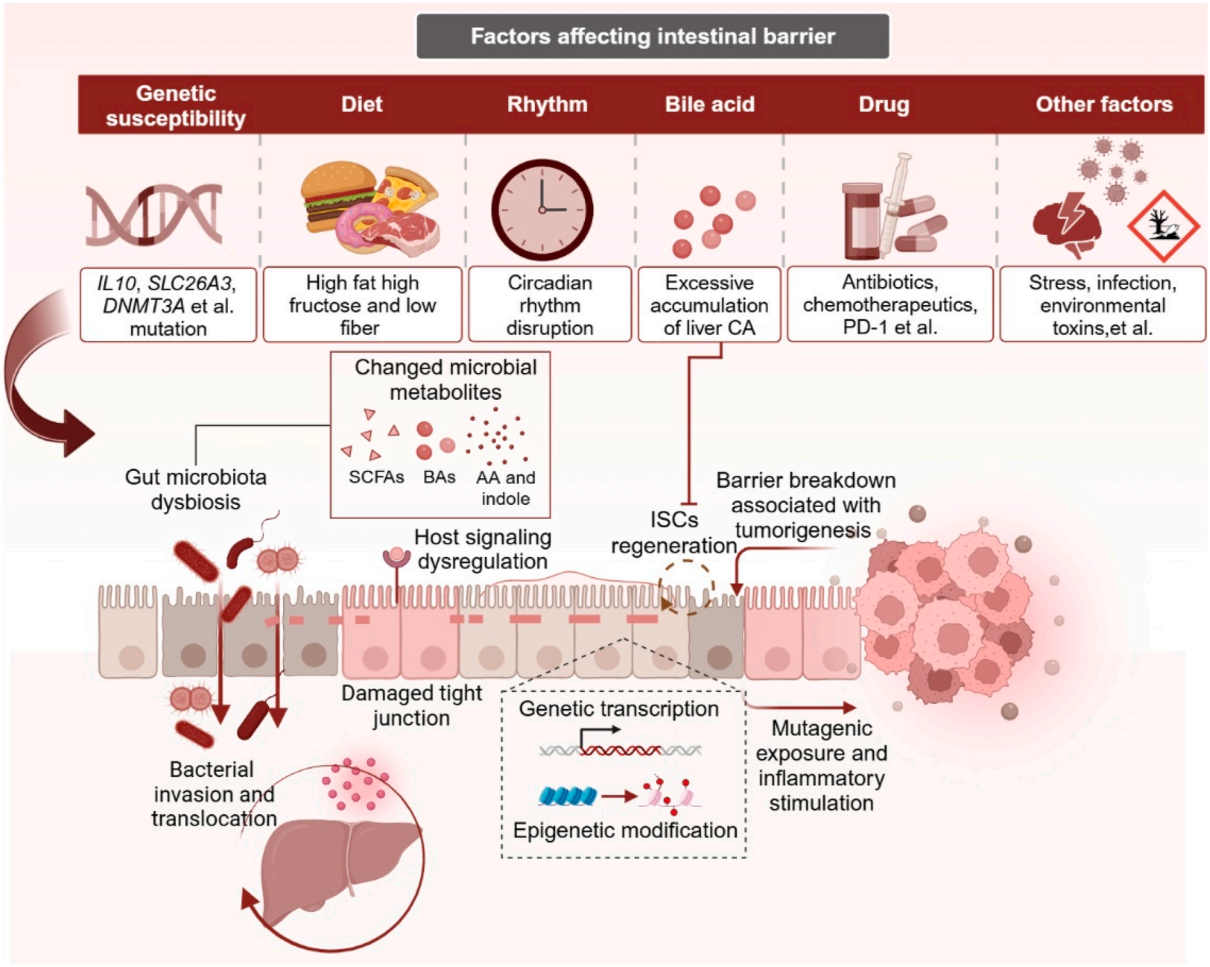

Figure 2 Factors affecting intestinal permeability and barrier function. The integrity of the intestinal barrier can be compromised by several factors, including genetic predisposition, western dietary preferences, use of antibiotics and other drugs, circadian rhythm disruption, and other internal and external factors. Inherited traits that may influence the structure and function of the intestinal barrier. Western dietary habits, characterized by high fat and sugar intake, can negatively impact gut health. Use of antibiotics and other medications can disrupt the balance of gut microbiota and compromise barrier function. Circadian rhythm disruption induced by irregular sleep patterns and unhealthy lifestyle factors can also influence gut health and permeability. Moreover, stress, infections, and environmental toxins can also play a role in degrading barrier integrity. The impairment of intestinal barrier can lead to microbial imbalance and a pro-inflammatory microenvironment. The resulting inflammation can further exacerbate intestinal barrier damage, creating a vicious cycle that contributes to the progression of various metabolic diseases. Created with Biorender.com.

TNF-α and other pro-inflammatory cytokines, thus exacerbating inflammation and weakening intestinal tolerance[66]. GWAS has also shown the significant downregulation of the *SLC26A3* gene, which encodes the DRA protein, an intestinal chloride anion transporter. This gene ranks among the top 1% of harmful IBD variants in the human genome[67,68]. Reduced expression of SLC26A3 significantly increases colonic paracellular permeability, lowers the expression of TJ and AJ proteins, and thus heightens susceptibility to IBD[69].

Additionally, glycoproteomic profiling has revealed that patients with congenital IBD may carry mutations in the *ST6GALNAC1* (*ST6*) gene, which encodes a sialyltransferase crucial for maintaining mucus barrier homeostasis. Mutations in this gene lead to a reduction in the thickness of the intestinal mucosal layer and disruption of its protective function[70]. Elucidating these regulatory mechanisms is important for comprehending the pathogenesis of congenital IBD. Furthermore, barrier function is also influenced by interactions of genetic predisposition and environmental factors. Mutations in DNA methyltransferase coding gene *DNMT3A*, which is associated with an increased risk of IBD, have been shown to reduce goblet cell number, shorten AJ complex, and increase intestinal permeability[71]. These changes increase susceptibility to colitis and hinter epithelial regeneration and repair processes.

3.2. *Bile acids*

Bile acids (BAs), which are the end products of cholesterol metabolism, act as natural emulsifiers that facilitate the absorption of intestinal lipids and the biliary excretion of cholesterol and phospholipids. Beyond these traditional functions, BAs also serve as hormones that regulate systemic metabolism and immune responses by binding to receptors such as Farnesoid X Receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). Recent studies emphasize the critical role of BAs in maintaining the

intestinal epithelial barrier. BA signals stimulate self-renewal of *Lgr5*$^+$ ISCs for intestinal barrier repair and homeostasis maintenance. However, excessive accumulation of the primary BA cholic acid in the intestine can impede *Lgr5*$^+$ ISC proliferation by hindering fatty acid oxidation *via* peroxisome proliferator-activated receptor (PPARα), thereby decelerating epithelial barrier repair[72]. Similarly, TGR5-mediated-signaling plays a vital role in preserving metabolic homeostasis, especially in the intestine where its expression is notably high. Activated by its natural ligand deoxycholic acid (DCA), a secondary BA metabolized from cholic acid, the TGR5 in ISCs triggers the transcriptional activation of downstream factors such as Yes-associated protein 1 (YAP1) and its regulator SRC, which collectively drive intestinal epithelial regeneration[73].

Furthermore, pregnane X receptor (PXR), a key bile acid-sensing nuclear receptor, modulates intestinal epithelial barrier homeostasis through its dual regulation of xenobiotic metabolism and innate immune regulation. Clinical studies have demonstrated significant downregulation of PXR and its downstream target genes in UC patients, suggesting that impaired PXR-mediated responses may contribute to defective barrier repair following intestinal injury[74]. PXR-deficient mice exhibit severe intestinal epithelial dysfunction and heightened susceptibility to multiple intestinal injury models[75]. The endogenous PXR ligand lithocholic acid (LCA) significantly attenuates pro-inflammatory signaling in necrotizing enterocolitis[76]. PXR activation mediates these protective effects by antagonizing the NF-κB pathway, suppressing pro-inflammatory cytokine release, and preserving TJ integrity during inflammation[77–79]. Bile acids function as endogenous ligands for the vitamin D receptor (VDR), exerting protective effects particularly in intestinal homeostasis[80]. VDR activation plays a crucial role in maintaining intestinal barrier integrity by regulating epithelial differentiation and enhancing TJ expression[81–83]. Furthermore, VDR signaling is essential for supporting Paneth cell antimicrobial function[84]. However, this protective mechanism becomes impaired during the pathogenesis of IBD and CRC. Clinically, dysregulation of the VDR signaling pathway is strongly associated with accelerated CRC progression and unfavorable clinical outcomes. Beyond its direct anti-proliferative effects on tumor cells, VDR activation contributes to CRC suppression by enhancing mucosal barrier integrity, thereby restricting tumor advancement[85,86].

3.3. Gut microbiota and derived metabolites

Under normal physiological conditions, the gut microbiota exists symbiotically with the host, primarily confined to the outer mucus layer by the intestinal epithelial barrier. Nevertheless, some microorganisms have evolved mechanisms to bypass this barrier, compromising the structural and functional integrity of the gastrointestinal tract. Although antibiotics might initially seem protective, their use is often counterproductive, as they can weaken the barrier function and increase the risk of new-onset IBD[87,88]. A population-based study in Sweden revealed a correlation between cumulative systemic antibiotic exposure and a higher risk of new-onset IBD[89]. In contrast, the gut microbiota has positive effects on intestinal barrier repair. By comparing with germ-free mice, the presence of gut microbiota promotes the growth of colon epithelial precursor cells *via* the signaling of activated macrophages within the stem cell niche to aid the restoration of damaged epithelial barriers in conventional mice, thus confirming their role in barrier repair[90].

The gut microbiota exerts their protective effects on the integrity of intestinal barrier by producing metabolites, including secondary BAs, which influence the function the intestinal barrier to impact overall gut health. In addition to BAs, clinical evidence has shown that the levels of another microbial metabolite tryptophan are significantly decreased in serum of patients with IBD[91]. Further studies suggest that alterations in the tryptophan metabolism are pivotal to disease progression and prognosis[92,93]. Tryptophan metabolites, specifically indole derivatives, serve as natural ligands for the aryl hydrocarbon receptor (AhR), which is widely expressed in the gut. AhR activation regulates regulatory T cells (Tregs) and Th17 cells, as well as the production of their cytokines, which are important for barrier protection, repair, and homeostasis maintenance, with IL-22 being a key effector. The kynurenine (Kyn) pathway, a major tryptophan metabolism route, is correlated with IBD progression[91]. Indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme in the Kyn pathway, promotes tryptophan metabolism to Kyn pathway under inflammatory conditions. IDO deficiency or inhibition can alleviate intestinal endotoxemia and chronic inflammation, as well as enhance intestinal mucosal and immune barriers, particularly in obesity models[94]. In addition to AHR activation, these metabolites enhance barrier integrity *via* PXR-mediated mechanisms. Specifically, indole-3-propionic acid (IPA) serves as an endogenous PXR agonist, attenuating intestinal permeability and inflammatory responses through TLR4 signaling[75]. Previous studies reveal that PXR activation preserves intestinal barrier integrity through coordinated mechanisms involving stabilization of TJ protein ZO-1 localization, suppression of myosin light chain kinase (MLCK) expression, and inhibition of JNK1/2 phosphorylation[79]. In summary, tryptophan-derived indole metabolites mediate dual protective effects on the intestinal epithelium through simultaneous activation of both PXR and AHR signaling pathways.

Short-chain fatty acids (SCFAs), another essential group of microbiota-derived metabolites, also support intestinal barrier function. SCFAs, such as butyrate, acetate, and propionate, are produced by the breakdown of dietary fiber by symbiotic flora, such as Firmicutes. These SCFAs act on the GPCRs, such as GPR43 or free fatty acid receptor 2 (FFAR2), to enhance the integrity of the intestinal barrier and protect CD8$^+$ T cells and DC cells from exhaustion and overactivation, thereby preventing the CRC development[95]. Butyrate, in particular, is known to inhibit histone deacetylases (HDACs) in the intestine to regulate gene transcription and aid in barrier restoration by modulating the actin-binding protein synaptopodin (SYNPO) at the TJ of colon epithelium and F-actin stress fibers[96]. GPCR signaling and HDAC inhibition are suggested to work together to maintain the integrity of the epithelial barrier. Furthermore, SCFAs stimulate goblet cells to secrete mucins, which in turn promote the growth of mucin-degrading bacteria to facilitate ISC differentiation into secretory lineages by consuming mucins, thereby ensuring a robust regenerative capacity for the epithelium[97].

3.4. Circadian rhythms

Circadian rhythms, often referred as the biological clock, are an internal control system for metabolic homeostasis, evolved to synchronize periodic environmental signals such as the light−dark cycle. This system orchestrates gene expression at specific times through transcriptional, post-transcriptional, and post-translational modifications to coordinate the optimal metabolic adaptation[98]. Several studies have demonstrated a strong correlation between

circadian disruptions and metabolic disorders. Specifically, irregular feeding schedules increase the exposure of small intestine to dietary antigens and microbial stimuli, resulting in a greater burden on the major histocompatibility complex II (MHC II) of IECs. Such disruption weakens the regulatory function of the intestinal microecology and diminish IL-10 secretion[99]. Circadian rhythms also impact neuroimmune circuits in the gut, which are activated by feeding behavior and can lead to pathological changes under dietary irregularities. Food intake triggers intestinal neurons to secrete vasoactive intestinal peptide (VIP), which upregulates proteins related to lipid absorption and transport. Concurrently, VIP reduces AMP levels in IECs and decreases the production of IL22 by ILC3[100]. Such disruptions in dietary rhythms facilitate intestinal colonization of pathogens, particularly when the barrier function of neuroimmune circuits is compromised[100].

Gut microbiota itself also exhibits circadian fluctuations in abundance and function, referred to as microbial oscillators, which impact the host circadian rhythm through microbial metabolites or autoantigens[101,102]. This interplay between the gut microbiota and host biological clock significantly influences barrier integrity and innate immune responses. For instance, SCFAs help regulate the circadian phase shift in the small intestine by inhibiting HDAC activity[103]. Segmented filamentous bacteria (SFB) in the gut drive rhythmic ILC3 circuit oscillations, in sync with host rhythm, thereby mediating diurnal alterations in infection resistance *via* time-dependent expression of AMPs[104].

3.5. Diet

The western diet, high in fat and sugar, is closely associated with the increased prevalence of metabolic diseases in western societies[105]. Dietary components significantly shape the gut microenvironment by altering the gut microbiome and the production of secondary metabolites that actively participate in host physiological processes[106]. Studies have shown that shifts in gut microbiota induced by the western diet raise DCA levels, which impair Paneth cells through activation of the intestinal FXR and type I interferon (IFN) signaling pathways[107]. Animal studies have further revealed that high-fat diet (HFD) exacerbates intestinal barrier damage across different colon cancer models, including the azomethane (AOM)-dextran sulfate sodium (DSS)-induced model as well as the *Apc*-mutation-induced spontaneous model. The HFD-compromised gut barrier allows more pathogens and derived metabolites to penetrate the epithelium, thereby accelerating CRC development[108].

In addition to high-fat intake, excessive dietary fructose consumption can also harm the epithelial barrier. Elevated fructose levels increase circulating endotoxins and thus activate toll-like receptor 4 (TLR4) on macrophages to trigger systemic inflammatory responses[109]. Glucose metabolism, meanwhile, presents both therapeutic potential for metabolic syndrome and a key coordinator of intestinal barrier function. In mouse models of type 2 diabetes mellitus (T2DM) with leptin deficiency (*ob*/*ob*) and leptin receptor (LepR) deficiency (*db*/*db*), hyperglycemia disrupts the intestinal barrier by inducing glucose transporter 2 (GLUT2)-dependent transcriptional reprogramming in IECs, which subsequently impairs the integrity of TJ and AJ structures[110].

3.6. Drug

The integrity of the gut barrier is intricately tied to the gut microbiome, with antibiotic usage, whether direct or indirect, profoundly affecting the abundance and structure of microbiota. The consequences of antibiotic therapy on host health arise from potential loss of immunomodulatory microbiota ligands, alteration in secondary metabolites, and signals related to specific microbiota[111]. Rifaximin-α, an antibiotic prescribed to prevent hepatic encephalopathy, safeguards the protective mucus membrane by reducing the population of sialidase-rich bacteria that break down mucus and increase levels of TNF-α and IL-17 in the gut microenvironment, which increases resistance to pathogens[112,113]. In addition, rifaximin-α treatment ameliorates stress-induced intestinal barrier dysfunction by enriching Lactobacillus levels in the lieum[114]. However, antibiotic treatment can also reduce gut microbiota diversity, causing immune dysregulation and increased susceptibility to infections. In healthy adult mice treated with a broad-spectrum antibiotic cocktail, dysbiosis occurred along with impaired epithelial TJ integrity, as indicated by reduced ZO-1 expression and activation of the NLRP3 inflammasome[87].

Non-antibiotic drugs can also disrupt the intestinal barrier. Aspirin, widely used for its anti-inflammatory and analgesic properties, is associated with gastrointestinal damage. It activates intestinal FXR signaling and decreases the abundance of *Parabacteroides goldsteinii*, a bacterium that produces 7-keto-LCA, which inhibits the stemness of ISC and slows barrier repair[115]. Chemotherapies are another major contributor to gut barrier damage. For instance, 5-fluorouracil accelerates mucosal cell death over regeneration. Consequently, more than 40% of chemotherapy patients experience gastrointestinal injuries, manifesting as symptoms such as diarrhea, constipation, and indigestion[116]. Immune checkpoint inhibitors (ICIs) that target programmed death receptor 1 (PD-1) have revolutionized antitumor therapy. Although these antibodies re-establish regular immune response by blocking the PD-1 pathway, they often cause gastrointestinal toxicities[117]. PD-1 signaling has been found essential for regulating colon lymphoid tissue inducer (LTi) cells, a specific subgroup of ILC3, which are crucial for maintaining immune homeostasis. Loss of PD-1 signaling results in the overactivation of fatty acid oxidation in LTi cells, and feedback inhibits both LTi cell activation and IL-22 production. This imbalance leads to dysbiosis, intestinal barrier damage, and increased susceptibility to enteritis[118].

4. Detection and analytical approaches of intestinal barrier integrity

In vivo assessment of intestinal barrier integrity can be performed through direct measurement of intestinal integrity, indirect analysis of biomarkers, and novel multi-omics-based analytical platforms. The assessment of intestinal permeability through urinary excretion of orally administered probe molecules represents a direct and widely utilized method. Typically, non-metabolized, poorly absorbed sugar probes, such as mannitol, rhamnose, sucralose, and lactulose, or low molecular weight polyethylene glycol (PEG) and ethylenediamine tetra-acetic acid (EDTA), are employed to evaluate intestinal barrier function[119]. To minimize potential interference from dietary sources, these probes are often isotope-labeled. Following oral administration, their urinary excretion rates are quantitatively assessed, serving as a reliable indicator of intestinal paracellular permeability[120]. The lactulose-mannitol test is a widely employed clinical assay for assessing intestinal barrier integrity. In this test, the urinary excretion of the large molecular weight lactulose serves as an indicator of leaky

gut, reflecting the extent of intestinal barrier dysfunction at sites of epithelial damage. In contrast, the small molecular weight mannitol is predominantly absorbed *via* transcellular pathways, representing non-specific epithelial transport[121]. Consequently, the lactulose-to-mannitol ratio (LMR) is a well-established biomarker for evaluating intestinal permeability[122,123]. In animal models, the absorption of FITC-labeled dextrans or chromium-51-labeled EDTA (^{51}Cr-EDTA) into systemic circulation is commonly used to assess intestinal barrier integrity[124,125] (Fig. 3)[1,55,119,120,122,125,126,128–131].

Furthermore, histopathological evaluation of endoscopic biopsy specimens allows for detailed examination of epithelial villous morphology and assessment of intestinal barrier integrity. Structural alterations in mucosal components can be systematically analyzed using mucin-specific Alcian Blue/Periodic Acid-Schiff (AB/PAS) staining for mucin layer evaluation, electron microscopy for ultrastructural analysis, and immunofluorescence techniques for precise localization and quantification of TJ protein expression.

Indirect assessment of intestinal barrier integrity utilizes a comprehensive biomarker approach combining serum diamine oxidase (DAO) levels as an indicator of mucosal injury, D-lactate measurement for permeability evaluation, bacterial endotoxin such as LPS detection to assess microbial translocation, and fecal calprotectin (FCP), lipocalin-2 (LCN2), and albumin quantification for monitoring inflammatory activity[122,126–131]. This approach is further enhanced by microbiome analysis, which provides systematic evaluation of the interconnected pathological features including mucosal damage, barrier dysfunction, and gut dysbiosis[122]. Recent advances in serum proteomics and genetic screening techniques have expanded the potential for early detection of barrier dysfunction while simultaneously supporting mechanistic investigations into its underlying causes[1,55].

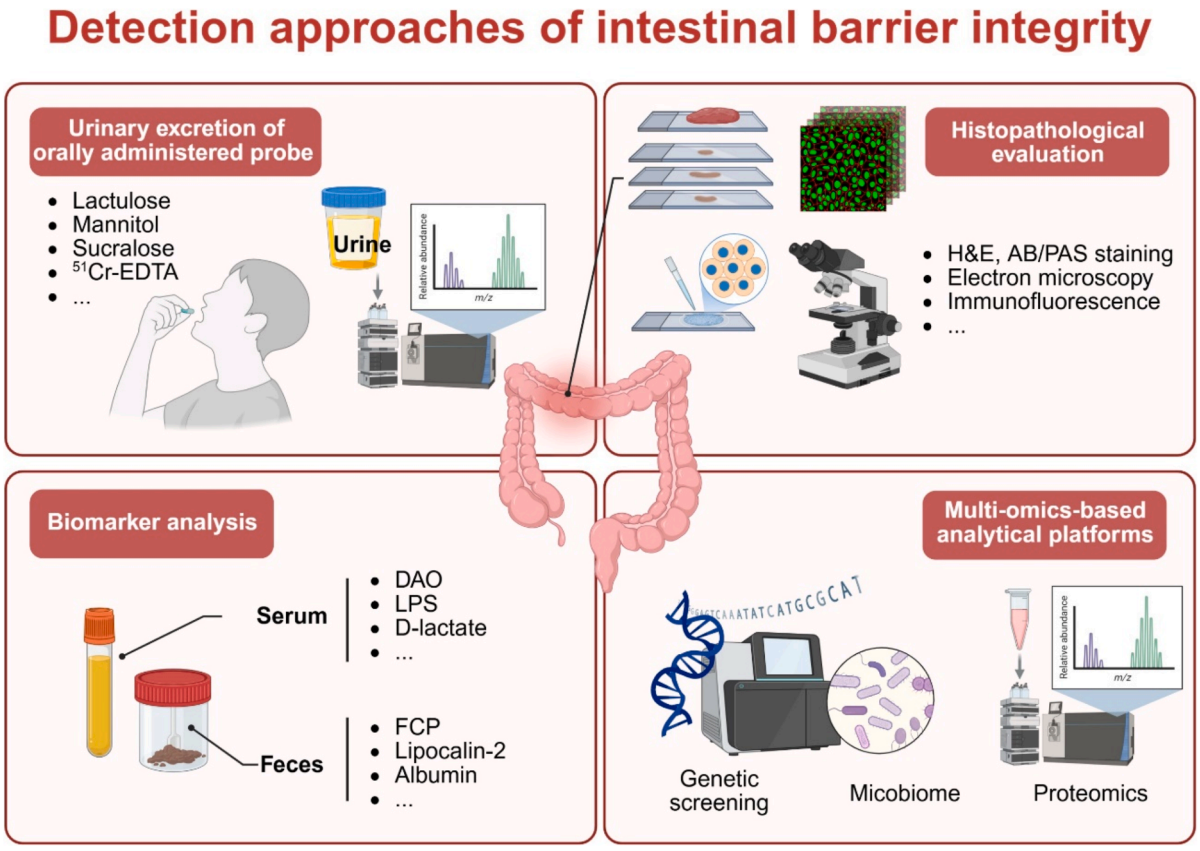

Figure 3 Measurements of intestinal barrier integrity. *In vivo* assessment of intestinal barrier integrity can be performed through direct measurement of intestinal integrity, indirect analysis of biomarkers, and novel multi-omics-based analytical platforms. Direct assessment of intestinal permeability employs established methodologies including urinary excretion quantification of orally administered probe molecules such as lactulose and mannitol, intestinal leakage evaluation *via* the lactulose-to-mannitol ratio (LMR), and systemic absorption measurement using chromium-51-labeled ethylene diamine tetraacetate (^{51}Cr-EDTA)[119,120,122,125]. Furthermore, histopathological examination of endoscopic biopsy specimens enables direct evaluation of mucosal architecture, including villi morphology and the spatial distribution and expression patterns of TJ proteins. Indirect assessment of intestinal barrier integrity utilizes a comprehensive biomarker approach combining serum diamine oxidase (DAO) levels as an indicator of mucosal injury[126], D-lactate measurement for permeability evaluation[128], bacterial endotoxin such as LPS detection to assess microbial translocation[131], and fecal calprotectin (FCP)[122], LCN2[129], and albumin[130] quantification for monitoring inflammatory activity. This approach is further enhanced by microbiome analysis[122], which provides systematic evaluation of the interconnected pathological features including mucosal damage, barrier dysfunction, and microbial dysbiosis. Recent advances in serum proteomics[1] and genetic screening techniques[55] have expanded the potential for early detection of barrier dysfunction while simultaneously supporting mechanistic investigations into its underlying causes. Created with Biorender.com.

5. Abnormal intestinal barrier function in the pathogenesis of gut and liver diseases

Dysregulation of the intestinal epithelial barrier is significant relevance to the development and progression of various gut and liver diseases. TJ dysfunction in the intestinal epithelium increases permeability, which facilitates the translocation of bacteria and their pathogenic factors across the barrier into systemic circulation and other tissues. This incursion triggers systemic inflammation and disrupts metabolic homeostasis, which are pivotal events in disease initiation and progression within the gut and liver. Although it remains uncertain whether the impairment of the intestinal barrier is a primary driver or a coincidental pathological feature, accumulating evidence suggests that the integrity of the intestinal barrier plays a critical role in the etiology of these diseases. A deeper understanding of the intrinsic and extrinsic factors that influence barrier function is necessary for unraveling the complex relationship between the intestinal barrier and disease pathology. This knowledge will provide directions for future research, leading to the identification of novel therapeutic targets that improve barrier function and address the root causes of gut and liver diseases.

5.1. *Inflammatory bowel disease and colorectal cancer*

IBD, including CD and UC, is characterized by chronic gastrointestinal inflammation, where epithelial barrier dysfunction is a key factor in disease onset and progression. Clinical studies show that altered intestinal TJ structures in UC and CD patients contribute to increased intestinal permeability[132]. Moreover, mucosal immune activation also leads to the production of cytokines such as TNF-α, IL-13 and IL-17. TNF-α induces epithelial barrier dysregulation by activating myosin light chain kinase (MLCK), which is considered a common regulatory pathway of acute TJ response to various immune and infectious stimuli[133]. IL-13 reduces barrier function and increases claudin-2 expression, which allows selective entry of solutes and ions, along with epithelial cell apoptosis, ultimately leading to TJ breakdown[50,134,135]. Further investigation suggests that increased paracellular permeability due to TJ dysfunction and cytoskeletal changes may precede the onset of disease, as seen in relatives of CD patients, who demonstrate early intestinal barrier irregularities and a higher prevalence of IBS[136−138]. Similarly, large-scale cohorts have identified markers of barrier impairment up to three years before CD diagnosis. This supports that barrier dysfunction is a primary cause in disease progression rather than a secondary effect[123].

Moreover, epithelial barrier defects expose the intestinal lining to mutagenic compounds or prolonged inflammatory stimuli, which may initiate and promote colorectal tumorigenesis through mechanisms such as oxidative stress[139]. In both early and advanced CRC, the expression of various barrier-related proteins is significantly reduced, which facilitates microbial translocation, triggers inflammation, and further accelerates tumor growth[140]. However, the precise mechanisms underlying the abnormal expression of epithelial barrier components during the initiation and development of CRC remain unclear. Indeed, experimental models show that mice with compromised epithelial barriers are more susceptible to colitis and inflammation-driven tumors. For instance, the loss of Golgi membrane protein 1 (GOLM1) overactivates the Notch pathway, and thus disrupts intestinal homeostasis, alters in the differentiation and secretory cell profile of IECs, and decreases the number of goblet cells, all of which increase intestinal permeability and pro-tumorigenic inflammation[141]. Mechanical barriers are also crucial in preventing CRC development. The tumor suppressor gene *N-myc* downstream-regulated gene 2 (*NDRG2*) has been shown to enhance the interaction between the E3 ligase FBXO11 and the E-cadherin inhibitor Snail, promoting Snail ubiquitination. This stabilization of E-cadherin strengthens AJs, thus limiting the development of colitis-associated tumors[142].

5.2. *Chronic liver diseases*

Chronic liver diseases, including MASLD, ALD, and PSC, are frequently encountered with compromised intestinal barriers and dysregulation of the intestine−liver axis[143]. Gastrointestinal substances, such as nutrients, secreted factors, and microbial metabolites, enter the liver *via* the portal vein and are metabolized for systemic utilization. This process renders the liver highly vulnerable to pathogen-associated molecular patterns (PAMPs), and makes it a primary target for enterogenic substances. In MASLD, endotoxemia is commonly observed, supporting the link between gut barrier integrity and liver inflammation. Similarly, DSS-induced gut barrier damage in mice leads to increased expression of pro-inflammatory genes and histological liver damage[144]. In western diet-fed, DSS-treated *Il-10* knockout mice, T-cell infiltration in terminal ileums coincides with decreased BA levels in the portal vein and liver. This BA reduction suppressed liver FXR signaling to exacerbate MASLD pathogenesis[145]. Gut dysbiosis, which compromises both the mucus layer and TJ integrity, has been identified as an early driver of MASH, as evidenced by metagenomic studies showing that gut microbiota dysregulation precedes liver disease onset in MASLDMASLD patients[146]. Moreover, previous studies revealed that fecal extracellular vesicles from MASH patients could decrease TJ expression *via* a non-myosin light chain kinase (nmMLCK)-mediated mechanism, aggravating intestinal barrier dysfunction[147]. Restoring the intestinal barrier in these cases can reverse liver lipid metabolism imbalances driven by colitis, particularly through the modulation of the secondary BA-TGR5/mTOR/oxidative phosphorylation pathway[145].

Additionally, alcohol exposure directly disrupts the integrity of the epithelial junction, and induces breakdown and dysfunction of intestinal barrier. Research demonstrates that the deficiency and inhibition of mitochondrial aldehyde dehydrogenase 2 (ALDH2), a key enzyme in alcohol metabolism, accelerate the binge drinking-induced degradation of intestinal TJ and AJ proteins, worsening intestinal epithelial dysfunction. Therefore, intestinal ALDH2 might be a potential target for alcohol-induced damage to the enterohepatic axis[148]. Chronic alcohol intake also decreases conventional type 1 dendritic cells (cDCs) in the intestine, but not in the liver. This consequently leads to the downregulation of AMP production, a decline in protective *A. muciniphila* abundance, the breakdown of AJs, and ultimately causes liver injury *via* the IL-12-IFNγ signaling pathway[149].

PSC is a chronic cholestatic and inflammatory liver disease, with 70%−80% of cases co-occurring with UC. PSC patients exhibit distinct gut microbiota profiles compared to healthy individuals. Moreover, the presence of microorganisms in the portal vein suggests intestinal barrier disruption, which may allow for bacterial translocation and the influx of microbial products into the liver[150]. Specific pathogenic bacteria, such as *Klebsiella pneumoniae* which are frequently detected in PSC patients, can induce the formation of monolayer epithelial pores through

contact-dependent apoptosis. This process lead to intestinal barrier damage, bacterial translocation, and activation of hepatichepatic Th17 cells, which exacerbates inflammation and increases the vulnerability to liver and biliary injury[151]. Furthermore, in a murine model of cholestatic liver disease induced by bile duct ligation (BDL), intestinal barrier disruption occurs independently of dysbiosis. Knockout of C/EBP homologous protein (CHOP), an apoptosis-promoting transcription factor regulated by ER stress, significantly alleviates intestinal barrier damage, loss of ISC stemness, as well as liver inflammation and fibrosis in BDL mice. This finding indicates the important role of ER stress-mediated gut−liver axis imbalance and barrier dysfunction in cholestatic liver injury[152]. Interestingly, in a chronic IBD model, damage to the intestinal barrier stimulates a protective negative feedback circuit in PSC, by which the endotoxin lipopolysaccharides activate the NF-κB pathway to suppress BA metabolism in hepatocytes, and then mitigates the progression of cholestatic liver disease[153]. Therapeutic interventions, such as antibiotics[151] or pan-caspase inhibitor IDN-7314[154], which attenuate dysbiosis-induced endotoxin translocation or NLRP3 inflammasome activation, have shown promise in treating PSC.

6. Potential interventions targeting the intestinal barrier

Immune-targeted therapies, including anti-inflammatory agents, immunosuppressants, and biologics, have proven effective in controlling inflammation in various intestinal diseases such as IBD. However, these treatments do not directly address the underlying damage to the intestinal barrier. Unfortunately, prolonged use of these medications may even increase the risk of infections, drug resistance, and disease recurrence, and serious adverse reactions, such as malignant tumors and death. Indeed, while reducing inflammation is crucial, promoting the healing and restoration of the epithelial barrier is pivotal for achieving long-term remission in intestinal disorders, especially IBD. Currently, no clinically approved therapies specifically target the repair and maintenance of the intestinal barrier. Given the close link between barrier dysfunction and the pathogenesis of both intestinal and liver diseases, timely repair and restoration of the epithelial barrier present a promising therapeutic strategy. Instead of focusing solely on symptom management, treatments that enhance epithelial healing and integrity could mitigate the progression of gut and liver diseases. Here, we summarized key therapeutic approaches for intestinal barrier restoration by targeting TJ adjustment, ecological regulation, ISCs regeneration, and immune regulation with supporting evidence from relevant clinical trials related to intestinal barrier integrity (Table 2). By strengthening the barrier, such therapies may also reduce bacterial translocation, inflammation, and the exacerbation of liver damage (Fig. 4)[72,73,97,157,158,162,169,170,174,180,183−186,188].

6.1. *Tight junction adjustment*

The maintenance of the intestinal barrier significantly relies on various TJ proteins. MLCK is considered a promising candidate target for developing barrier therapeutics for IBD duo to its central role in regulating TJs and their breakdown. Deletion or inhibition of MLCK can effectively protect the barrier function from immune-induced damage, but these interventions do not prevent advanced colitis, which involves apoptosis and mucosal damage that occur independent of MLCK-mediated TJ breakdown. These findings reflect the therapeutic limitations of MLCK inhibitors[155]. Current MLCK inhibitors also lack specificity towards the catalytic domain of epithelial and smooth muscle MLCK, thus resulting in potential toxic side effects[156].

Potential targets for TJ regulation include occludin and claudin, both of which are important for sustaining intestinal integrity. A study on protein tyrosine phosphatase (TCPTP) activity in epithelial cells showed that TCPTP protects the intestinal barrier by directly restricting STAT1-mediated transcription of the cation-selective pore claudin-2, as well as upregulating inhibitory matriptase, which prevents occludin mislocalization and decreases epithelial permeability[157]. However, there are currently no clinical trials testing medicines specifically targeting TJ proteins. This implies the need for further research and development in this area.

6.2. *Ecological regulation of gut microbiota and the host-microbiome interaction*

Probiotics have been found to regulate barrier function through multiple mechanisms. For instance, *Lactobacillus reuteri* activates the Wnt/β-catenin signaling pathway to induce Paneth cell differentiation and AMP secretion, and meanwhile stimulates the proliferation of *Lgr5*$^{+}$ ISCs to promote epithelial repair[158]. Additionally, flagellin from *Roseburia* spp. binds to Toll-like receptor 5 (TLR5), which can upregulate occludin and MUC2, thereby improving intestinal barrier integrity and increasing IL-22 and REG3γ levels to further regulate gut ecology[159]. *Akkermansia muciniphila* also supports intestinal epithelial repair, proliferation, differentiation, and stability *via* the regulation of ISC program[97]. Therefore, targeting intestinal microbial dysbiosis emerges as a promising therapeutic strategy for restoring impaired barrier function. Recent advancements include genetically engineered probiotics coated with overexpressed artificial enzymes using biological nanomaterials, a novel approach to mucosal repair and inflammation therapy[160,161]. *Bifidobacterium longum*, modified to express catalase and superoxide dismutase, demonstrates enhanced colonization of the intestines, robust anti-inflammatory activity, facilitates intestinal barrier remodeling, and regulates the microbial balance. These developments could potentially reduce the adverse reactions of traditional anti-inflammatory drugs[162].

BAs serve as a crucial mediator in host-microbiota communication and the regulation of gut microbiome composition[163]. Dysregulation of BA synthesis is strongly associated with the pathogenesis of various diseases. Activation of FXR effectively mitigates the detrimental effects of BA overload by inhibiting cholesterol metabolism and promoting BA transportation from hepatocytes, thereby reducing cholestatic liver damage. Studies have shown that the FXR agonist obeticholic acid (OCA) can increase the proportion of microbes involved in DNA synthesis and amino acid metabolism, reduce the proliferation of certain Gram-positive bacteria, and decrease the concentrations of endogenous bile acids, thus effectively improving gut ecological disorders[164]. OCA treatment also prevents damage to the intestinal vascular barrier by stabilizing β-catenin within endothelial cells[165].

AHR, a receptor for tryptophan metabolites, plays an important role in maintaining the integrity of the intestinal barrier. Studies have revealed a significant loss of epithelial barrier function in *Ahr*$^{-/-}$ mice, characterized by destruction of the intestinal mechanical barrier and a failure to commit to a differentiating lineage[166]. Notably, this phenotype is also observed in mice with an AHR ligand-deficient diet. Subsequent research

Table 2 Clinical trials related to intestinal barrier strengthening.

Class	Intervention	Disease	Effect on intestinal barrier function	Trial registration number
Gut ecological regulation	Rifaximin-α (550 mg BID)	Hepatic encephalopathy	↑Faecal TNF-α, IL-17E, and IL-17A enriched intestinal microenvironment; ↓Circulating neutrophil TLR-4 expression and plasma TNF-α ↓Species with mucin-degrading capacity in faeces	NCT02019784
	FMT from healthy donors	DSPN	↑ZO-1, Claudin-1, Claudin-4 in the colonic mucosa ↓Serum LBP, IL-6, TNF-α	ChiCTR1800017257
	Non-absorbable, gut-restricted, engineered carbon bead adsorbent Yaq-001	Cirrhosis	↓Gut permeability in the organoids	NCT03202498
Immune regulation	IL-22 Fc fusion protein UTTR1147A	UC	↑Ducible epithelial genes *DMBT1*, *MUC1*, *STAT3,* *MUC4*, *REG1A*, *and REG3A* ↓Baseline dysbiosis	NCT02749630
	Proline hydroxylase domain (PHD) inhibitor	IBD	Preclinical IBD models show ↓Plasma FITC-dextran ↑Barrier-protective genes *Tff3*, *Tjp1*, *Nt5e* ↓proportions of monocytes, neutrophils and proinflammatory $CD3^+$ T cell subsets; ↓IL-17 signaling, fecal lipocalin 2 (LCN2) and calprotectin levels ↓Plasma IL-6 and TNF	CTR20241789, NCT06012578
	Transglutaminase 2 inhibitor ZED1227	Celiac disease	↓Ratio of villus height to crypt depth ↓Intraepithelial lymphocyte density, Celiac Symptom Index score, and Celiac Disease Questionnaire score (100-mg dose)	EudraCT 2017-002241-30
Dietary intervention	Gluten-free diet	Irritable bowel syndrome-diarrhea	↓Bowel movement, 0−2 h levels of mannitol and LMR; ↑ZO-1, claudin-1, occludin in small bowel mucosa	NCT01094041
	Resistant starch intervention	Overweight or obesity	↓MCP-1, IL-1β, IL-6; ↑anti-inflammatory IL-10 in serum and mWAT; ↑TJ expression including ZO-1, Occludin; ↓Serum DX-4000-FITC, LPS in serum and mWAT	ChiCTR-TTRCC-13003333
	Crohn's disease exclusion diet (CDED) coupled with partial enteral nutrition (PEN)	Mild to moderate Crohn's disease	↑Proportion of patients with normal LMR; ↓Serum level of C-reactive protein and fecal level of calprotectin; ↓Fecal *Proteobacteria*	NCT01728870
	Oral glutamine intervention	Post-infectious diarrhea in irritable bowel syndrome	↓LMR; ↓Irritable Bowel Syndrome Severity Scoring (IBS-SS) scores; ↓Daily bowel movement frequency and Bristol Stool Scale	NCT01414244

demonstrated that AHR ligands derived from diet could effectively prevent diseases that impair barrier function by upregulating the expression of TJ proteins *via* promoting intracellular Zn^{2+} signaling[167]. Other AHR agonists, such as Urolithin A (UroA), a microbial metabolite, exhibit promise in protecting the barrier function. UroA has anti-inflammatory activity and promotes barrier repair by activating the AhR−NrF2-dependent pathway to upregulate TJs[168]. These studies demonstrate the importance of intestinal AHR pathway-dependent activation in the treatment of ALD, a highly associated form of liver disease characterized by loss of TJ barriers[169,170]. These findings suggest AHR may serve as a valuable therapeutic target for intestinal barrier repair, especially in chronic diseases associated with barrier dysfunction.

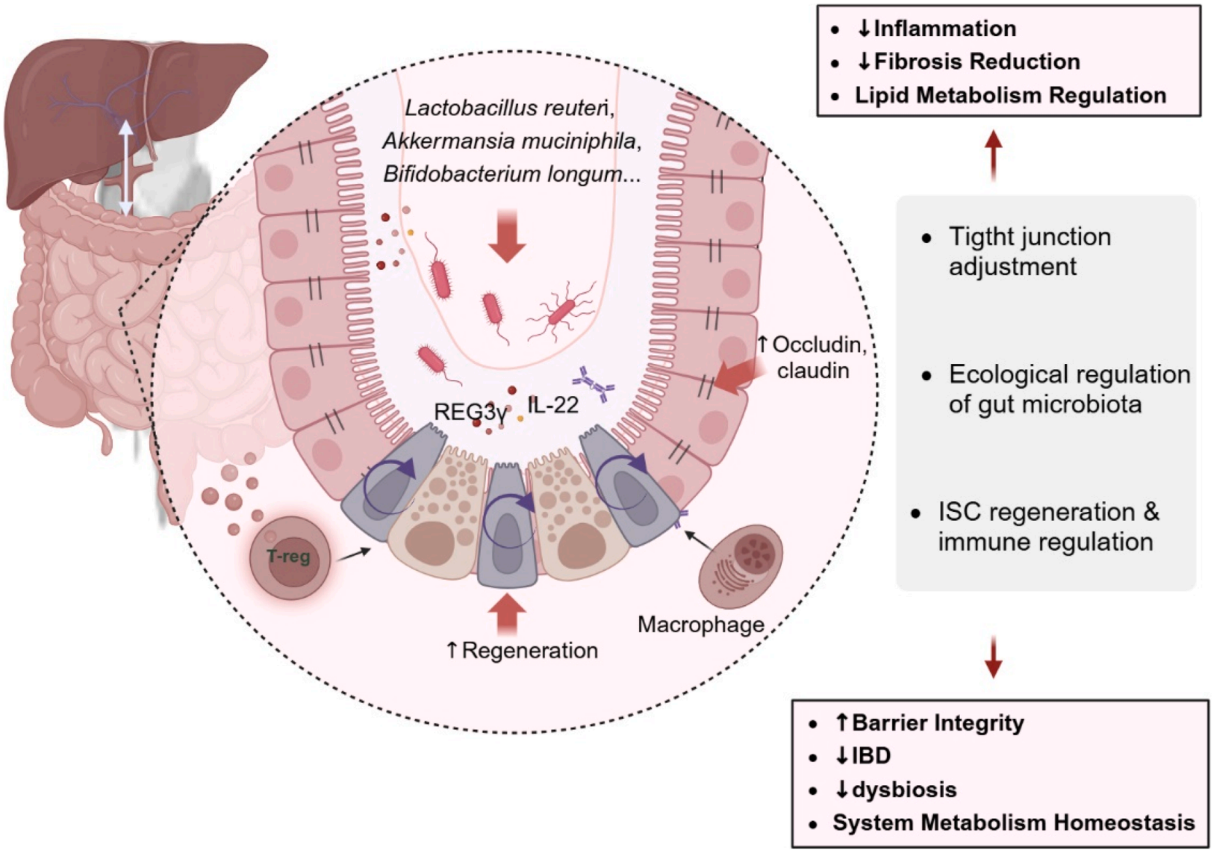

Figure 4 Potential interventions targeting the intestinal barrier to enhance the management of chronic gut and liver diseases. While immune-targeted therapies, such as anti-inflammatory agents, immunosuppressants and the biologics, can effectively reduce intestinal inflammation, they often carry the risk of serious side effects and fail to directly address barrier damage. This limitation will cause the lack of long-term cure for the disease. Therefore, it is necessary to develop effective therapeutic strategies for the timely repair of the intestinal epithelial barrier. Studies targeting TJs, ecological regulation of gut microbiota, intestinal stem cell regeneration, and immune regulation have shown potential value in enhancing enterohepatic function. Targeting intestinal epithelial TCPTP has been demonstrated to preserve intestinal barrier integrity by modulating TJ components, including normalizing claudin-2 expression and maintaining localization of ZO-1 and occludin[157]. Probiotic administration (*e.g.*, *Lactobacillus reuteri*, *Akkermansia muciniphila*, *Bifidobacterium longum*)[97,158,162] and microbial metabolites[169,170,174], such as tryptophan derivatives, can restore intestinal barrier integrity by enhancing *Lgr5*$^{+}$ ISCs proliferation and upregulating levels of TJ proteins, MUC2, AMPs represented by REG3γ. Emerging therapeutic strategies targeting ISCs regeneration, including modulation of the bile acid−FXR axis and organoid-based transplantation, hold significant promise for ameliorating chronic enterohepatic diseases[72,73,180]. Additionally, immune signaling pathways mediated by cytokines such as IL-10[183,184] and IL-22[185,186,188] have been identified as potential therapeutic targets for enhancing intestinal barrier integrity. Created with Biorender.com.

The inhibition of IDO, an enzyme that catalyzes the conversion of tryptophan to Kyn, has shown potential for treating barrier dysfunction. By diverting tryptophan towards indole metabolism, IDO inhibition can increase the production of AHR ligands, which are beneficial for intestinal integrity. While IDO inhibitors demonstrated favorable outcomes in cancer therapy[171], their application in managing intestinal barrier damage requires further investigation. The IDO inhibitor indoximod has been shown to effectively preserve tight intercellular connections and significantly improve DSS-induced colon injury[172]. However, it is important to consider that IDO inhibition might also induce adverse enterotoxic effects, suggesting that complete blockade of the Kyn pathway may, paradoxically, compromise epithelial barrier integrity. Studies have shown that chemotherapeutics-induced intestinal damage triggers an upregulation of tryptophan−Kyn−kynurenic acid pathway, which promotes the production of kynurenic acid in gut, and subsequently feeds back to activate GPR35 to enhance intestinal integrity[173]. These findings imply that indiscriminate inhibition of Kyn pathway could dampen this GPR35-mediated protective response by reducing kynurenic acid levels, and potentially decelerate the barrier repair. Such complexities of tryptophan metabolism in gut health suggest the need for comprehensive research when developing new therapeutic strategies targeting intestinal barrier dysfunction.

While substantial research has demonstrated that direct modulation of gut microbiota improves intestinal barrier function and ameliorates enterohepatic diseases, microbial-based therapies remain limited in clinical practice. The intestinal barrier-enhancing properties of microbiome-derived beneficial metabolites, such as indole-3-lactic acid (ILA), are contingent upon host-specific microbiome regulation[174]. Clinical efficacy is fundamentally determined by baseline host microbiota composition, which governs both microbial colonization dynamics[175]. Furthermore, host genetic variation constitutes a critical determinant of

therapeutic outcomes. For instance, IBD patients carrying CARD9 risk alleles exhibit impaired microbial conversion of dietary tryptophan into AHR-activating metabolites[176]. These findings elucidate the molecular basis for the substantial interindividual variability observed in microbiota-targeted therapies. Probiotics, as symbiotic microorganisms depleted during disease states, require a stable host microenvironment for colonization and function. Without prior restoration of the impaired gut ecosystem, microbial intervention therapies often fail to establish durable microbial equilibrium or achieve meaningful clinical outcomes[177]. Consequently, future therapeutic strategies should adopt a dual-target approach combining microbial modulation with microenvironment restoration, designed to synergistically re-establish gut ecological balance and promote epithelial barrier healing.

6.3. *Intestinal stem cell regeneration*

The renewal, repair, and regeneration of intestinal epithelium are heavily dependent on *Lgr5*$^+$ ISCs, located at the crypt base. *Lgr5*, a specific marker for ISCs, encodes receptors that can trigger the reprogramming of ISCs into epithelial lineages in response to signals such as Wnt[178]. ISC activity, regulated by both extracellular and paracrine signals, maintains homeostasis and initiates adaptive differentiation in response to injury to ensure the fundamental physiological functions of the intestine. BAs play a crucial role in mediating gut−liver communication and integrate dietary and metabolic signals that regulate ISC function[73]. Recent studies have shown a novel intervention for treating IBD-associated intestinal damage by reducing excessive BA accumulation in gut under pathological conditions. FXR agonist treatment reduces the enterohepatic levels of cholic acid by suppressing CYP8B1 expression in the liver, and thus alleviates the BA-related toxicity on *Lgr5*$^+$ ISCs[72]. These findings suggest the feasibility of targeting ISCs to treat IBD based on cross-organ metabolic regulation.

The significant role of ISCs in injury repair and self-renewal has also led to the exploration of ISC culture and transplantation to the site of injury as a therapeutic strategy for repairing damaged mucosa. For instance, colon organoids derived from *Lgr5*$^+$ ISCs successfully restore damaged rectal epithelium through enema transplantation[179]. Moreover, transplantation of ileum-derived organoids into colons has shown potential in creating functional small intestinalized colon (SIC) tissue, which retains regional characteristics such as absorptive functions, presenting promise for the treatment of short bowel syndrome (SBS)[180]. The therapeutic applications of organoids, with their ease of *in vitro* culture and physiological resemblance to native tissue, have opened new avenues in regenerative medicine. However, there are many translation challenges that need to be addressed, such as efficient *in vivo* delivery, potential immune rejection, and the long-term stability of transplanted cells. These issues warrant further investigation. The potential of intestinal organoids in regenerative medicine is vast, and continued research in this field might lead to substantial breakthroughs in the treatment of gastrointestinal and extra-intestinal diseases.

6.4. *Immune regulation*

Traditional anti-inflammatory therapies, including corticosteroids, 5-aminosalicylates, and the novel TNF-α monoclonal antibodies, have been the standard treatments for IBD and other immune-mediated disorders. While these therapies effectively reduce inflammation and alleviate symptoms, they often fall short in achieving long-term healing, particularly in relation to the intestinal barrier. Many patients experience a loss of response over time and disease recurrence. For instance, although anti-IL-6 antibody therapy was effective in moderate to severe CD or UC in clinical trials, serious adverse reactions such as abscesses and intestinal perforations continue to occur in some patients[181]. These therapies often fail to address the underlying epithelial dysfunction, which is a key factor in sustaining chronic intestinal inflammation.

To address these limitations, there is growing interest in targeting immune pathways that are more directly involved in epithelial barrier repair. IL-10 is an effective anti-inflammatory and tissue-regenerative cytokine[182], and recent IL-10 preparations have been developed with the goal of enhanced therapeutic effects by targeting mucosal barriers[183,184]. Another promising target is IL-22, which has its receptor IL-22R expressed on intestinal epithelial cells, making IL-22 and IL-22R potential candidates for therapies aimed at restoring epithelial integrity and enhancing mucosal healing. IL-22 plays a pivotal role in maintaining intestinal homeostasis by stimulating the production of AMPs and mucins, as well as ISC regeneration. Consequently, IL-22 is considered a potential therapeutic approach for barrier repair. IL-22 controls the generation of Paneth cell generation, thereby increasing intestinal levels of AMPs[185]. Moreover, IL-22 initiates the transcription of IL-18 *via* STAT3 phosphorylation, which promotes the proliferation and repair capability of *Lgr5*$^+$ ISCs and the bacterial clearance by IFN-γ^+ T cells *via* Akt−Tcf4 signaling pathway to enhance the epithelial barrier defense[186].

The IL-22 fusion protein agonist Efmarodocokin alfa (UTTR1147A) is currently under investigation for active UC and CD treatment (NCT02749630). Clinical trials have shown that UTTR1147A activates IL-22R signaling pathways in both UC patients and healthy individuals, with improvements in UC-associated dysbiosis[187]. Furthermore, specific activation of IL-22 signaling in the gut can enhance hepatic and systemic glucose and lipid metabolic homeostasis in a microbiota-dependent manner in models of metabolic disorders[188]. Additionally, IL-22 has also demonstrated positive effects on MASLD, ALD and dietary obesity[159,189]. When administered exogenously, IL-22 exerts its therapeutic effects through its receptor on IECs, rather than hepatocytes, and then activates STAT3 and inhibits WNT−β-catenin signaling to reduce the absorptive enterocyte compartment. Nonetheless, the role of IL-22 in intestinal barrier maintenance remains controversial, with concerns over possible pathogenic immunomodulatory effects, such as mediating CXCR2$^+$ neutrophil chemotaxis in colonic tissue and increasing resistance to the IL-23 monoclonal antibody Ustekinumab. These observations indicate that IL-22-targeted therapies might not always achieve the desired efficacy, necessitating further research to better understand the full impact and potential side effects of IL-22 activation.

IL-17A, mainly produced by Th17 cells, mediates inflammatory infiltration and the recruitment of immune cells. Although anti-IL-17A monoclonal antibodies have been used to treat autoimmune diseases, their application in IBD has led to significant adverse reactions and, in some cases, disease exacerbation. Research has revealed the essential role of IL-17A signaling in the expression of ATOH1, the key transcription factor that regulates the differentiation of *Lgr5*$^+$ISCs into secretory cell lineages vital for maintaining mucosal epithelial integrity[190]. This observation highlights the challenges of relying solely on immunotherapy, as

blocking IL-17A signaling, can disrupt epithelial homeostasis and further induce drug resistance and disease recurrence. Additionally, potential immune targets for promoting mucosal healing include CXCL1 production mediated by intestinal PTGER4^{+} macrophages, which has been associated with enhanced tissue repair. Furthermore, macrophage-derived TGFB1 has been shown to activate pro-regenerative transcription factors such as YAP/TEAD and SOX9, which promote epithelial regeneration *via* signaling pathways critical for ISC function[191]. Therefore, a deeper understanding of intercellular communication mechanisms, particularly among immune cells, ISCs, and intestinal secretory cells, will be necessary in the future. The approach, which combines the synergistic actions of immune and regenerative signals, holds great promise for the development of next-generation treatments for IBD and other gut and liver disorders.

6.5. Potential advances in clinical trials related to intestinal barrier function strengthening

Multiple innovative therapies targeting intestinal barrier integrity are currently undergoing clinical validation (Table 2). The novel gut-restricted selective prolyl hydroxylase domain (PHD) inhibitor ISM5411, developed using a multimodal generative artificial intelligence platform, has successfully completed Phase I trials (CTR20241789, NCT06012578). Preclinical studies demonstrate the dual mechanism of this drug in intestinal mucosal repair and immune regulation, showing significant efficacy in IBD models[192]. Global multicenter trials are now planned to further validate these therapeutic benefits. Clinical evidence demonstrates that Rifaximin-α effectively enhances intestinal barrier repair by modulating the gut microenvironment through upregulation of TNF-α and interleukin-17E in feces, thereby strengthening antimicrobial defenses against pathogenic invasion (NCT02019784)[112]. Furthermore, fecal microbiota transplantation (FMT) from healthy donors has shown therapeutic potential in restoring intestinal barrier function and mitigating systemic inflammation in diabetic distal symmetric polyneuropathy (DSPN)[193]. A non-absorbable, gut-restricted, engineered carbon bead adsorbent Yaq-001 exhibits clinically relevant efficacy in cirrhosis by ameliorating gut barrier dysfunction and reducing systemic endotoxin burden (NCT03202498)[194]. Dietary interventions for barrier repair have demonstrated efficacy across multiple gastrointestinal conditions. Clinical studies show benefits in irritable bowel syndrome-diarrhea (NCT01094041)[195], metabolic disorders (ChiCTR-TTRCC-13003333)[196], and mild to moderate Crohn's disease (NCT01728870)[197]. Notably, dietary glutamine supplementation significantly restored intestinal permeability and alleviated post-infectious diarrhea in irritable bowel syndrome (NCT01414244)[198]. In celiac disease, the transglutaminase 2 inhibitor ZED1227 demonstrated significant improvement in duodenal mucosal architecture, including villous height and crypt depth, while reducing intraepithelial lymphocyte infiltration. The therapeutic mechanism involves inhibition of glutamine residue deamidation in immunogenic gluten peptides, thereby preventing the activation of T cell and subsequent mucosal injury (EudraCT 2017-002241-30)[199,200]. Engineered probiotics demonstrate significant therapeutic potential for restoring intestinal barrier integrity and maintaining mucosal homeostasis. Current research focuses on combining their barrier-enhancing properties with immunomodulatory effects, though clinical translation remains at the preclinical stage. While these advances underscore the promise of targeted barrier repair strategies, comprehensive evaluation of long-term safety and efficacy in human trials is needed to advance clinical applications.

7. Conclusions and perspectives

The intestinal barrier is a complex and dynamic structure that maintains gut homeostasis, mediates host-microbiome interactions, and shields against pathogens and toxins. Its dysfunction is central to the development of many gastrointestinal diseases, including IBD, and extra-intestinal conditions such as obesity and MASLD. Emerging research on gut−X communication emphasizes the need for therapeutic strategies that not only reduce inflammation but also promote epithelial barrier repair. While advances in immunosuppressive and biologic therapies for IBD and related disorders have improved symptom management, they often fail to address the root cause of barrier dysfunction. Prolonged use of these treatments can lead to significant side effects, including infection risks, malignancy, and disease recurrence, suggesting the need for a paradigm shift toward therapies that integrate barrier-restorative strategies with traditional anti-inflammatory approaches. Stem cell-based regeneration, microbial therapy, bile acid modulation, and TJ modulators are promising for achieving durable disease remission.

Intestinal barrier dysfunction exhibits a complex bidirectional causality with disease pathogenesis, serving as a primary trigger initiating pathological cascades or as a consequence exacerbating disease progression. This dynamic interplay is critically influenced by genetic susceptibility, environmental exposures, and stage-specific diseases. As a pathogenic cause, intestinal barrier dysfunction precedes overt pathological manifestations and initiates disease processes through diverse mechanisms mediated by genetic predisposition, dietary factors, circadian rhythm, drug usage, and other environmental influences. Disruption of the mucus layer and TJ structures enables pathogenic bacteria and their metabolites to translocate into systemic circulation, triggering inflammatory response and multi-organ dysfunction that ultimately contribute to the pathogenesis of MASH, metabolic disorders, IBD, CRC, ALD, and PSC. Intestinal barrier injury is also a pathological consequence and disease amplifier, generating multi-organ pathological cascades through gut dysbiosis, immune hyperactivation, and metabolite toxicity. These mechanisms exacerbate conditions including IBD, MASH, PSC, and CRC. Furthermore, the resulting disease microenvironment reciprocally impairs barrier integrity, establishing a self-perpetuating vicious cycle of pathophysiology.

There is accumulating clinical evidence of off-target and systemic side effects from immunosuppressive therapies, including the loss of treatment efficacy, exacerbated inflammatory damage, and immune disorders[201]. Inflammatory cytokines can directly damage the epithelial barrier to aggravate inflammation, and necessitate anti-inflammatory interventions. However, these same cytokines also trigger essential regenerative signals that promote mucosal healing[202]. Immunosuppressive therapies may block these beneficial signals, and thereby inhibit the barrier repair process, worsen microbial imbalances, and further damage epithelial integrity. This interplay between therapeutic benefits and adverse effects complicates disease management, leading to clinical recurrence and treatment failure. While our understanding of epithelial barrier structure and function has advanced, the etiology of barrier damage and the complex network mechanisms

involved in intestinal mucosal healing remain unclear. The further exploration into intercellular communication among intestinal cells, immune, non-immune, host, and microbial, will be crucial for identifying more effective targets.

The transition from NAFLD to MASLD identified the significant role of global metabolic dysfunction in the pathogenesis of fatty liver diseases[203,204]. Increasing evidence suggests that the loss of intestinal barrier homeostasis, which is important for systemic metabolic balance, is closely linked to liver diseases[205]. Consequently, repairing the intestinal barrier is now recognized as integral to treating liver disease, and the gut−liver axis has emerged as a promising therapeutic target. This has led to the novel concept of "enteric treatment for liver disease", with the BA-intestinal FXR signaling pathway demonstrating considerable efficacy in MASLD treatment[206,207]. Furthermore, there are still many unknown enterohepatic communication secretory proteins and metabolites that warrant further exploration.

In addition to pharmacological treatments, regenerative medicine has progressed rapidly with the development of stem cell-derived organoids. These organoids, which can be cultured and transplanted to mimic the functional properties of *in vivo* tissue, offer new possibilities for repairing damaged gut epithelium. They hold particular promise for conditions where endogenous regeneration is insufficient, such as refractory IBD or SBS. However, challenges remain in the therapeutic application of organoids, such as ensuring functional integration, preventing immune rejection, and achieving long-term stability post-transplantation. Looking ahead, a comprehensive approach combining ISC-targeted therapies, microbial modulation, immune regulation, and organoid-based regeneration offers a multifaceted pathway to improve outcomes in diseases linked to intestinal barrier dysfunction. Future research should focus on developing precise interventions that work synergistically with existing treatments to promote barrier repair, restore homeostasis, and prevent relapse.

When translating experimental data to human disease pathogenesis, it is crucial to carefully evaluate the animal models used. The DSS colitis model specifically induces damage to the intestinal epithelial barrier through TJ dependence, but it fails to reflect the damage observed in non-TJ dependent regions of the human intestinal tract in conditions as IBD. Meanwhile, the types and abundance of barrier injury markers used in animal models must align with the clinical characteristics of patients to ensure the translational relevance of experimental findings.

Barrier defense and repair, independent of immunosuppression, is a valuable objective for treating hepatoenteric diseases. Specific intestinal barrier disorders vary across diseases and individuals, suggesting that personalized treatment strategies may be more effective. Enhancing intestinal barrier integrity has been shown to have great potential in preventing and reversing liver steatosis, immune infiltration and fibrosis in MASLD[208]. For milder conditions, improvements and prevention can be achieved through dietary or non-pharmacological methods, such as probiotics and related products. In the future, human studies will be critical to validate these potential targets and treatments (Table 1)[37,64−70,72,73,89,95−97,99,106,108,113,118,133,134,136−138,140,146−148,151−153,209].

In conclusion, restoring the intestinal barrier represents is not only a therapeutic challenge, but also a significant opportunity. By addressing the fundamental defects in epithelial integrity and the complex interactions that maintain it, we stand on the verge of a paradigm shift in the treatment of intestinal and systemic diseases. The convergence of novel biotechnologies, regenerative medicine, and microbiome research promises to reshape the landscape of gastrointestinal therapy and holds great potential to improve patient outcomes.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

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