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Impact of intestinal immunologic barrier dysfunction on perioperative complications

Wenxin Shi, Yajun Hu, Jin Lan, Jun Xiong, Zhiyong Li

Department of Pathology, Faculty of Medical Imaging, Naval Medical University, Shanghai 200082, China.

Corresponding authors: Jun Xiong and Zhiyong Li.

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Highlights

- Intestinal barrier dysfunction increases the risk of perioperative complications.
- The immunologic barrier is crucial for maintaining intestinal homeostasis.
- Perioperative factors compromise the intestinal immunologic barrier, increasing infection risk.
- An imbalance between intestinal microbiota and immune cells affects postoperative recovery.
- Clinical intervention studies targeting the intestinal barrier are summarized.

Abstract

Intestinal barrier dysfunction plays a critical role in perioperative complications, especially in the circumstances where immunologic barrier is damaged. This paper reviews the structure of the intestinal immunologic barrier, its interaction with intestinal microbiota, and its effects on intestinal epithelial cells. It emphasizes the key role of the intestinal immunologic barrier in maintaining intestinal homeostasis and explains how its dysfunction increases the risk of infection, anastomotic leakage, gastrointestinal motility disorders, and systemic inflammatory response syndrome during the perioperative period.

Keywords: Intestinal barrier, perioperative complications, immunologic barrie

Introduction

The intestinal barrier is a critical defense system that maintains intestinal microenvironment homeostasis. It comprises the mechanical, chemical, immunologic, and microbial barriers, which collectively preserve intestinal integrity. Among them, the immunologic barrier is crucial in preserving intestinal homeostasis and preventing pathogen invasion [1]. Intestinal immune cells serve as sentinels within the intestinal microecosystem, exhibiting a remarkable capacity to rapidly recognize and clear invading pathogens [2]. In addition to preventing infections, these cells regulate the renewal and repair of intestinal epithelial cells by releasing various cytokines and signaling molecules [3, 4]. This multifaceted immune function reinforces the intestinal barrier, effectively impeding the translocation of harmful substances into the abdominal cavity or systemic circulation [1]. A delicate dynamic equilibrium exists between intestinal immune cells and the intestinal barrier [1]. In a healthy gut microbiome, immune cells remain in a state of vigilant quiescence to avoid overreacting and harming symbiotic microbes. However, disruptions in the intestinal microbiota, particularly an increase in pathogenic bacteria, trigger an immediate activation of immune defense mechanisms. This rapid immune response facilitates pathogen clearance, restores intestinal microecological balance, and preserves intestinal barrier function and stability [3].

Address correspondence to: Jun Xiong, Department of Pathology, Faculty of Medical Imaging, Naval Medical University, Xiangyin Road, Yangpu District, Shanghai 200082, China. E-mail: xiongjun2001@163.com; **Zhiyong Li**, Department of Pathology, Faculty of Medical Imaging, Naval Medical University, Xiangyin Road, Yangpu District, Shanghai 200082, China. E-mail: zhiyongli@smmu.edu.cn.

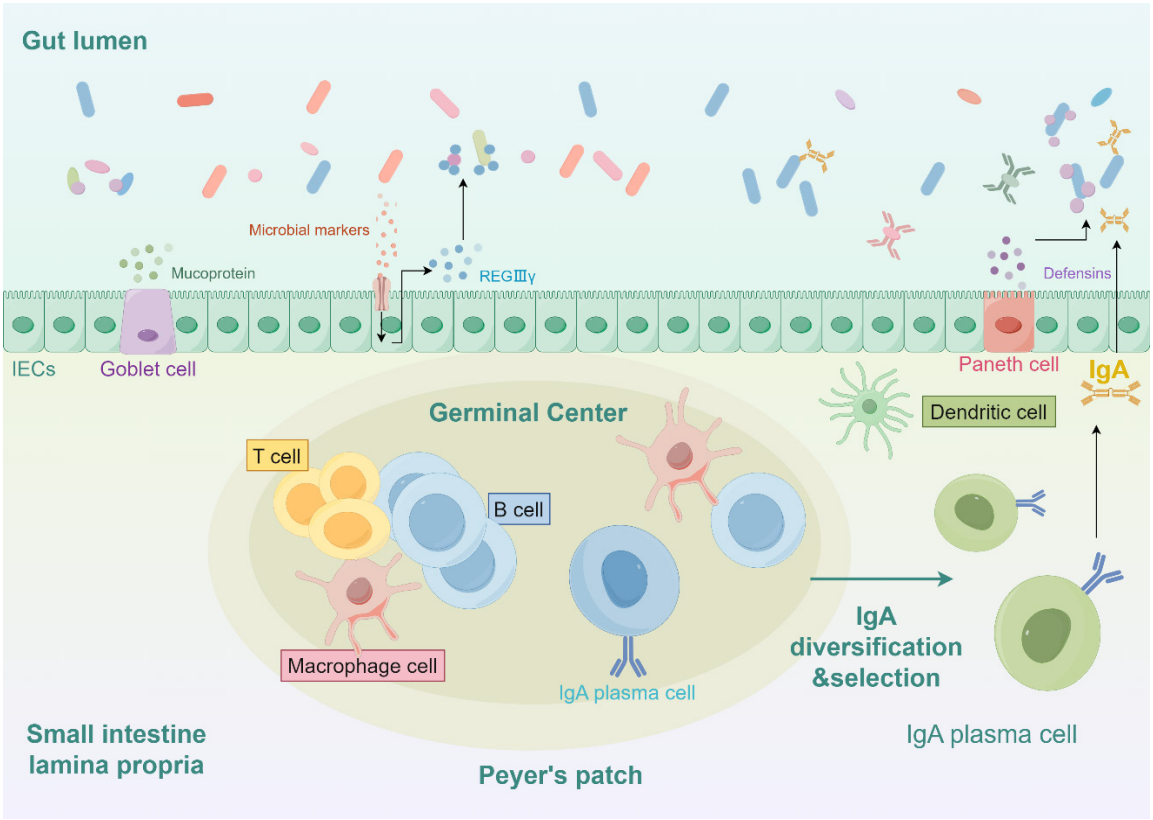

Figure 1. Intestinal barrier composition.

With advances in surgical techniques, and clinical care, surgical outcomes have significantly improved. However, recovery from major surgeries is often disrupted by unpredictable postoperative complications [5]. These complications, including infections, anastomotic leakage, gastrointestinal dysmotility, malabsorption, and cancer recurrence, can substantially impede patient recovery and outcomes [5]. Emerging evidence indicates that disturbances in the balance between the gut microbiome and intestinal immune cells play a crucial role in elevating the risk of postoperative infections [3]. Postoperative infection represents a critical turning point, often leading to severe complications such as anastomotic leakage and systemic inflammatory response syndrome (SIRS) [5]. The intestinal immune cell barrier emerges as a key determinant in this process. This review aims to elucidate the perioperative alterations in the intestinal immune cell barrier and their consequential impact on postoperative recovery following major surgical interventions.

The intestinal immunologic barrier: A complex defense system

Structure of intestinal immunologic barrier

The intestinal barrier represents a sophisticated, multi-layered defense system crucial for maintaining gastrointestinal homeostasis. It consists of three primary components: the biological barrier (gut microbiota), the mechanical barrier (intestinal epithelial cells and their tight junctions), and the immunologic barrier (immune cells within the intestinal mucosa and lamina propria, as well as gut-associated lymphoid tissue (GALT)) [1]. The structure and distribution of the intestinal barrier are shown schematically in **Figure 1**. These interconnected elements work synergistically to facilitate nutrient absorption while preventing pathogen invasion and maintaining mucosal integrity [1].

Within the intestinal epithelium, specialized structures such as Peyer's patches harbor critical immune cells derived from both innate and adaptive immune systems, including thymus-derived T cells, bone marrow or synovium-derived B cells, dendritic cells, and macrophages. Furthermore, antimicrobial peptides secreted by Paneth cells and secretory immunoglobulin A (IgA) produced by plasma cells further fortify the mucosal defense [6]. Paneth cell-derived antimicrobial peptides directly combat bacterial intrusion, while IgA forms a protective layer on the mucosal surface, preventing pathogen adherence and invasion [6]. Peyer's patch is highlighted in **Figure 1**. The intestinal vascular (endothelial) barrier constitutes another protective layer, which effectively limits the translocation of microorganisms and their by-products into the systemic circulation [7]. GALT plays a

pivotal role in immune surveillance, recognizing and responding to foreign antigens within the gut lumen. This lymphoid tissue serves as a primary site for initiating immune responses. The collaboration of various immune cell populations establishes a robust defense mechanism: T cells recognize and eliminate infected or malignant cells; B cells neutralize pathogens through antibody production, particularly IgA; and antigen-presenting cells, such as dendritic cells and macrophages, act as sentinels, engulfing and presenting antigens to activate adaptive immune responses [7]. These details are demonstrated in **Figure 1**.

The integrity of this multi-faceted barrier system is paramount for maintaining health. Intestinal mucosal barrier dysfunction and increased permeability enable bacteria or toxins to enter the blood or lymphatic channels in the circulatory system, leading to SIRS. When treatment is inappropriate or not timely, the condition may progress to multiple organ dysfunction syndrome [8]. In this pathophysiological cascade, the immunologic barrier plays a critical role in modulating the inflammatory response and preventing systemic complications.

The microbial barrier is the outermost barrier of the intestinal tract. The chemical barrier is close to the microbial barrier and is a layer of mucous membrane. Physical barrier, also known as mechanical barrier, includes the mucosal epithelium, lamina propria, and muscularis mucosae. Mucosal epithelium has an inherent epithelium, including immune cells and enterocytes, and is reinforced by tight junctions. Beneath the lamina propria, the immunologic barrier is composed of immune cells located within the mucosa and lamina propria, as well as the GALT. The gut vascular barrier is the deepest protective layer of the intestinal tract. The intestinal immunologic barrier, depicted in detail, reveals a sophisticated network of immune components. Peyer's Patches, crucial immune structures within the intestinal epithelium, serve as aggregation sites for key innate and adaptive immune cells, including T and B lymphocytes. Paneth cells contribute to the barrier function through the secretion of antimicrobial peptides, while plasma cells produce secretory IgA, both playing pivotal roles in mucosal immunity. The GALT houses Foxp3+ regulatory T cells, dendritic cells, and macrophages, all of which synergistically maintain intestinal immune homeostasis. The right panel elucidates the diversity and selection process of IgA, highlighting its role in recognizing and responding to a broad spectrum of antigens and pathogens, thereby serving as a critical component of the intestinal immune defense system.

Intestinal immunologic barrier and intestinal microbiota

The human gut microbiome comprises a diverse community of microorganisms, including bacteria, fungi, and viruses [9]. Most of these microbes are commensal bacteria that benefit the host by aiding digestion and competing with pathogens for colonization sites [10]. To distinguish between commensals and pathogens, intestinal epithelial cells (IECs) and innate immune cells, including dendritic cells and macrophages, utilize specialized mechanisms known as pathogen-recognition receptors [11]. These receptors include toll-like receptors, nucleotide-binding and oligomerization domain (NOD)-like receptors, and RIG-I-like receptors, which recognize microbial markers, such as bacterial DNA, flagellin, and components of bacterial cell wall [12, 13]. These microbial markers persistently stimulate IECs to produce antimicrobial agents, including regenerating islet-derived protein III-γ, angiogenin-4, and cytokines such as IL-33 and IL-25 [14]. These molecules play crucial roles in maintaining intestinal homeostasis and promoting the development of tolerogenic immune cells [15]. Consequently, this intricate interplay between the microbiome and host immune system preserves symbiotic relationships and maintains microbial equilibrium within the gut ecosystem.

Patients with inflammatory bowel disease exhibit impaired pathogen recognition due to aberrant expression of pattern recognition receptors. Frameshift mutations in the NOD2 gene, a member of the NOD-like receptor family expressed in the cytosol of IECs, have been identified in patients with Crohn's disease (CD) [16]. Studies in NOD2-deficient mice revealed compromised goblet cell function and elevated interferon-gamma production by intraepithelial lymphocytes. Furthermore, these mice displayed an enrichment of commensal Bacteroides species, potentially contributing to mucosal inflammation [17]. Thymic stromal lymphopoietin (TSLP), produced by IECs in response to commensal microorganisms such as Gram-negative Escherichia coli or Gram-positive *Lactobacillus rhamnosus*, represents another critical regulator of intestinal immunity [18]. TSLP upregulates CD40, CD80, and CD86 expression on dendritic cells via the signal transducer and activator of transcription signaling pathway, promoting the differentiation of non-inflammatory TH2 cells or regulatory T cells [19]. Study by Taylor et al. demonstrated increased production of IL-12/23p40 and interferon-gamma in TSLP

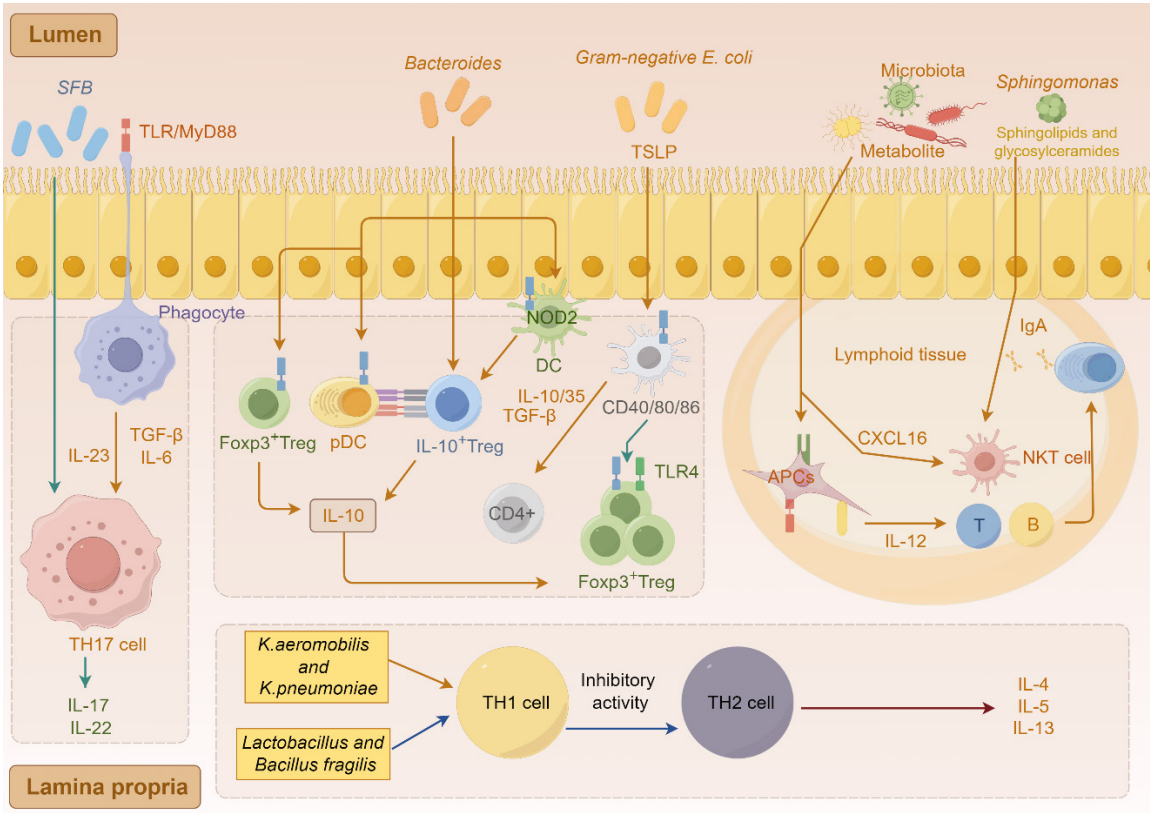

Figure 2. The influence of intestinal microorganisms on the development of intestinal immune cells.

receptor-deficient mice during acute intestinal inflammation induced by dextran sodium sulfate [20]. This finding suggests that excessive IL-12 production by dendritic cells can inhibit TH2 cell development. Notably, in CD patients, IECs often fail to produce TSLP, leading to uncontrolled IL-12 release and subsequent disruption of intestinal homeostasis.

The gut microbiota profoundly influences the function and activity of diverse T cell subpopulations, including Th1, Th2, Th17, and regulatory T cells [3]. Specific bacterial genera have been shown to modulate distinct T cell responses. For instance, colonization of germ-free mice with *Klebsiella* species (*K. aeromobilis* and *K. pneumoniae*) induces Th1 cell proliferation and expansion in the gut [21]. Conversely, certain strains of Lactobacillus and Bacillus fragilis inhibit Th2 activity by enhancing Th1 responses [22]. Th2 cells, which produce interleukins IL-4, IL-5, and IL-13, play crucial roles in humoral immunity, defense against helminth, and chronic inflammatory conditions such as allergies and asthma [23]. Th17 cells, in contrast, are potent pro-inflammatory immune cells implicated in autoimmune and inflammatory disorders [23]. Th17 cell differentiation is predominantly initiated by the cytokines transforming growth factor (TGF)-β and IL-6 and sustained by IL-23 [24]. Research has shown that Gram-positive segmented filamentous bacteria, also known as *Candidatus arthromitus*, promote Th17 cell development and the secretion of various cytokines such as IL-17 and IL-22 [25]. Conversely, Treg cells facilitate immune tolerance through contact-dependent mechanisms and the production of immunomodulatory cytokines such as IL-10, TGF-β, and IL-35 [26]. Regulatory T cells are broadly categorized into induced regulatory T (iTreg) cells and natural regulatory T cells [27]. Recent studies have identified five *Bacteroides* species (*B. intestinalis*, *B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, and *B. massiliensis*) capable of effectively inducing colonic Treg cell development [28]. These findings underscore the complex interplay between the gut microbiota and T cell subpopulations in maintaining intestinal homeostasis and modulating immune responses.

Metabolites produced by the gut microbiota play a crucial role in modulating T cell development and function, facilitating rapid responses to intestinal stimuli and promoting adaptive immune responses [3]. Recent studies have elucidated specific mechanisms by which microbial metabolites influence various T cell subsets. For instance, Luu et al. demonstrated that valerate, a short-chain fatty acid produced by *Megasphaera massiliensis*, regulates IL-12 synthesis in antigen-presenting cells, thereby modulating CD8+ T lymphocyte activation [29]. Natural killer T (NKT) cells, another important component

of the intestinal immune system, are activated by microbial antigens such as sphingolipids and glycosylceramides [30]. Furthermore, microbial-derived bile acids have been shown to influence NKT cell accumulation in the liver by mediating CXCL16 expression. Notably, *Clostridium species* can alter bile acid composition, leading to elevated CXCL16 levels in hepatic sinusoidal endothelial cells [31]. In contrast, *Fusobacterium varium* significantly suppresses a broad spectrum of genes associated with bile acid metabolism, resulting in a marked reduction of both CD4+ and CD8+ T cell populations [32]. These findings underscore the complex interplay between gut microbial metabolites and the host immune system. Various gut microbiota can respectively enhance the growth and differentiation of Th1, Th2, Th17, Treg, T, and NKT cells. The connection between the flora and cells is clearly depicted in **Figure 2**.

Th1 cells: *Klebsiella* species, specifically *K. aeromobilis* and *K. pneumoniae*, promote the proliferation and expansion of Th1 cells within the gut. Th2 cells: *Lactobacillus* and *Bacillus fragilis* have been shown to suppress Th2 activity by enhancing Th1 responses. Th2 cells are primarily responsible for the production of interleukins such as IL-4, IL-5, and IL-13. Th17 cells: The differentiation of Th17 cells is primarily initiated by cytokines TGF-β and IL-6, with IL-23 playing a crucial role in sustaining this process. Segmented Filamentous Bacteria play a crucial role in the development of Th17 cells and the secretion of various cytokines, including IL-17 and IL-22. Treg cells: Treg cells help maintain immune tolerance through both contact-dependent mechanisms and the production of immunomodulatory cytokines such as IL-10, TGF-β, and IL-35. Species within the *Bacteroides* genus, including *Bacteroides intestinalis*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, and *Bacteroides massiliensis*, are known to induce colonic Treg cells. CD4+ T cells: TSLP produced by Gram-negative Escherichia coli influences CD4+ T cells through the signal transducer and activator of transcription signaling pathway. CD8+ T cells: The metabolite valerate controls the synthesis of IL-12 by antigen-presenting cells and affects the activity of CD8+T cells. NKT cells: Sphingolipids and glycosylceramides produced by *Sphingosinomonas* activate NKT cells. Microbial bile acids mediate the expression of CXCL16 and affect the accumulation of NKT cells.

Intestinal immunologic barrier and intestinal epithelial cells

The gastrointestinal tract is perpetually exposed to a diverse array of dietary and bacterial antigens, necessitating a robust immune defense against potential external threats. The intestinal epithelium plays a pivotal role in limiting antigen exposure to immune cells, thereby preventing hyperactive immune responses [33]. Serving as the primary defense mechanism of the intestine, epithelium is characterized by a sophisticated structure that forms a meticulously regulated barrier. This barrier comprises a monolayer of tightly packed columnar epithelial cells, interconnected by tight junctions [33]. While tight junctions contribute to the physical barrier, specialized IECs, such as goblet cells and Paneth cells, play crucial roles in antimicrobial defense and are integral to the innate immune system [2]. **Figure 3** provides an overview of the intestinal mucus barrier and its related cellular activities.

Secretory IECs, including goblet cells and Paneth cells, establish the intestinal mucus barrier by secreting mucus and antibacterial proteins. This barrier primarily consists of gel-like mucins, such as mucin-2 and mucin-6, secreted by goblet cells. These mucins are glycoproteins that form an intricate network, effectively impeding pathogen penetration [34]. The mucosal architecture of the small intestine and large intestine exhibits distinct structural differences. The mucus layer in the small intestine is relatively loose and thin, whereas the mucus layer in the colon is notably thicker and stratified into inner and outer layers. While the outer mucus layer of the small intestine allows bacterial penetration, the inner colonic mucus layer adheres firmly to the epithelial surface, preventing bacterial invasion [35]. Additionally, goblet cells produce molecules such as clover factor 3, which support mucosal recovery and repair [36]. Another product of goblet cells, the Resistin-like molecule β, is upregulated in response to Th2 cytokines during nematode infections [37]. Paneth cells contribute to this defense by producing antimicrobial peptides, with defensins being the most abundant [38]. Human α-defensins 5 (HD5) and 6 (HD6) are particularly significant. HD5 disrupts bacterial plasma membranes and is effective against both Gram-positive and Gram-negative bacteria, while HD6 encapsulates bacteria in a “straitjacket,” thereby restricting their activity until they lose viability [39]. Chu et al. demonstrated that HD6 can bind to bacteria and self-assemble into a nanonet, effectively countering *Salmonella typhimurium* [40]. In CD patients, the expression levels of both HD5 and HD6 are notably down-regulated [41]. Paneth cells also secrete lysozyme, a potent glycosidase that hydrolyzes peptidoglycan in bacterial

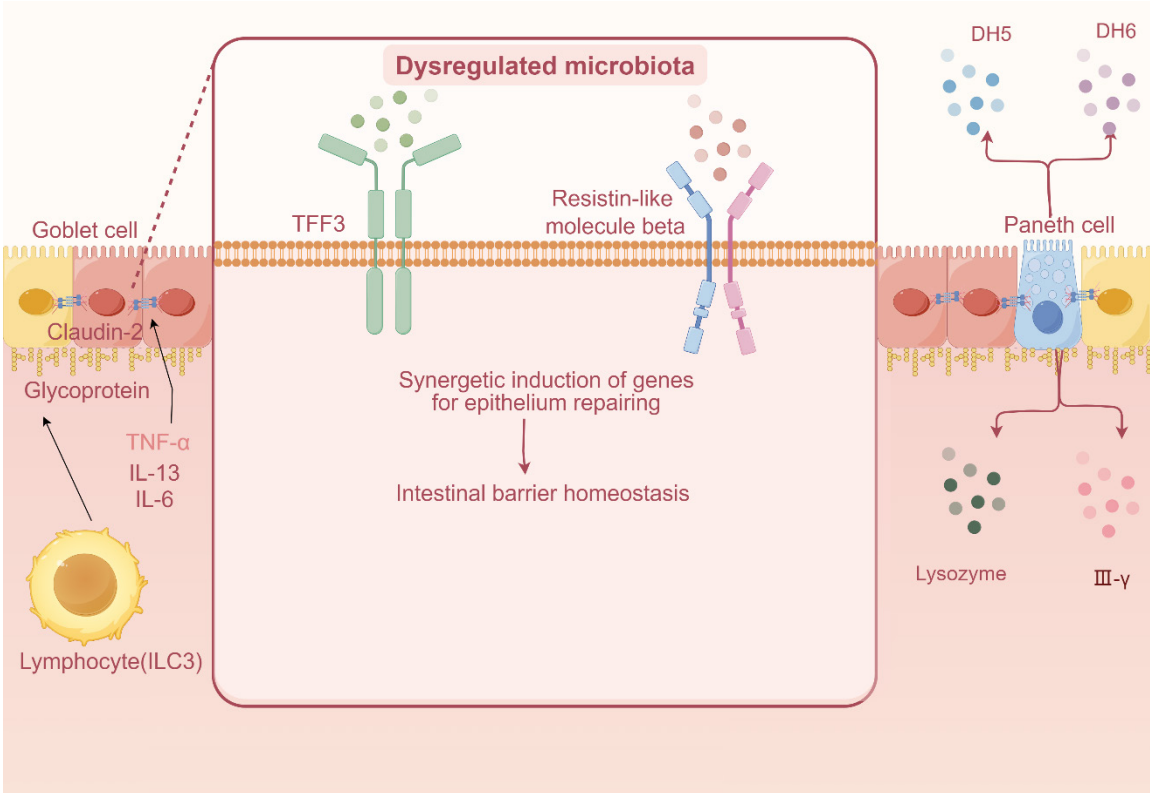

Figure 3. Immune function of the intestinal epithelium.

cell walls, thereby exerting potent antibacterial effect [42]. Additionally, Paneth cells produce regenerating islet-derived protein III-γ, which similarly targets bacterial cell wall [42]. Research has demonstrated that mice deficient in regenerating islet-derived protein III-γ exhibit persistent inflammatory responses [43]. Moreover, the intestinal epithelium also contributes to intestinal immune system maturation by delivering antigens to immune cells in a regulated manner. Microfold (M) cells, located in the follicle-associated epithelium and distributed from crypts to villi, internalize microbes and antigens from the gut lumen and transport them to immune cells in GALT. This process is crucial for the development and regulation of intestinal immune system [44].

Pro-inflammatory cytokines play a significant role in modulating intestinal tight junction function and maintaining barrier integrity [45-48]. IL-13 has been strongly correlated with the upregulation of Claudin-2, a protein involved in forming pore-like channels between IECs [45, 46]. In Caco-2 cells, a widely utilized model of IECs, stimulation with IL-1β induces a redistribution of occludin, another TJ protein, and increases the expression of myosin light chain kinase [47]. Innate lymphoid cells type 3 (ILC3) induce glycosylation of IECs, facilitate their normal differentiation, and enhance interactions with symbiotic bacteria. A deficiency in ILC3 results in differentiation defects and impaired barrier function [48].

Disruption of homeostasis significantly elevates the risk of autoimmune diseases and chronic inflammation [49]. Deficiencies in proteins such as FADD, which regulates cell death, can result in programmed necrosis of IECs, potentially leading to chronic enteritis [50]. Additionally, imbalances in IEC renewal and replacement mechanisms can result in excessive antigen invasion, triggering intestinal inflammation, as observed in ulcerative colitis and CD [49].

Goblet cells are responsible for secreting glycoproteins that play a crucial role in preventing pathogen penetration. Additionally, they produce trefoil factor 3, which plays a crucial role in epithelial cell repair. Additionally, goblet cells secrete Resistin-like molecule beta, contributing to immune function. Paneth cells, on the other hand, secrete anti-microbial peptides, with defensins being the most abundant. The two significant defensins in humans are HD5 and HD6. Furthermore, Paneth cells release lysozyme and lectins, which facilitate the production of regenerating islet-derived protein III-gamma, an enzyme that hydrolyzes peptidoglycans in bacterial cell walls. IL-6, IL-13, and tumor necrosis factor (TNF)-α have been shown to upregulate Claudin-2 expression. ILC3 are capable of inducing glycosylation of intestinal

epithelial cells and facilitating their normal differentiation. A deficiency in ILC3 results in abnormalities in epithelial cell differentiation.

Potential harm to the intestinal immunologic barrier during the perioperative period

The perioperative period encompasses the crucial stages before and after surgical procedures, during which patients' physiological states undergo significant fluctuations, making it a high-risk interval susceptible to various complications. Recent advancements in medical research have increasingly demonstrated a significant association between dysfunction of the intestinal immunologic barrier and perioperative complications.

Preoperative period

Malnutrition

Preoperative malnutrition has been identified as a factor that compromises the intestinal immunologic barrier, thereby elevating the risk of postoperative complications [51]. A study by Mingwei indicated that the concentrations of diamine oxidase, D-lactic acid, and endotoxin on postoperative days 3 and 7 were significantly reduced in patients receiving enteral immunonutrition, compared to the control group, which did not receive immunonutrition [51]. Additionally, on day 7 post-surgery, patients in the study group exhibited lower peripheral blood white blood cell counts and neutrophil to lymphocyte ratio, alongside elevated albumin levels. These findings suggest that enteral immunonutrition may help mitigate systemic inflammatory responses. [51]. One month after surgery, the study group also showed a significant increase in CD4+T and CD8+T cell counts, indicating a long-term positive effect of enteral immunonutrition on cellular immune function [51].

Stress reaction

Psychological and physiological stressors have a substantial influence on intestinal barrier function, particularly in pigs, which are considered an ideal model for investigating diseases linked to early life adversity. The pig model provides a deeper understanding of how psychological stressors affect gut barrier function and their long-term consequences during ontogenesis. By employing the pig early weaning stress (EWS) model, studies have explored its impact on intestinal health and function from different perspectives [52–55]. In the study of Medland et al., female EWS pigs at 60 and 170 days of age exhibited a significantly heightened response to veratridine-induced short-circuit current when compared to a late-weaning control group [55]. This response was inhibited by specific neurotoxins, suggesting an enhancement in secretomotor neuron function. Additionally, the number of choline acetyltransferase-positive intestinal neurons in the ileum was higher in EWS pigs, along with enhanced cholinergic signaling. This was accompanied by a downregulation of mucosal muscarinic receptor 3 gene expression, which may be associated with the regulation of intestinal function. Pohl et al. demonstrated that, in comparison to the late-weaning control group, EWS pigs exhibited a higher incidence of chronic functional diarrhea, increased intestinal permeability, and elevated mast cell counts during both juvenile and adult stages [54]. These findings underscore the long-term detrimental effects of EWS on porcine intestinal health.

The study by Ziegler et al., which examined the impact of environmental adaptation on intestinal barrier function in pigs subjected to transport stress, revealed that adapted pigs showed significantly enhanced permeability of intestinal macromolecules within one hour of initial in vitro incubation, suggesting that environmental adaptation may exacerbate intestinal permeability [52]. However, unacclimated pigs displayed superior wound-healing capabilities and more consistent recovery of transepithelial resistance, indicating that stress may facilitate the effective repair of the intestinal barrier. Subsequent analyses revealed that acclimated pigs demonstrated diminished expression of the tight junction protein claudin-4 during the recovery phase, whereas unacclimated pigs exhibited enhanced localization of this protein in the apical membrane. These findings further support the hypothesis that acute stress may expedite the repair of the intestinal barrier. Xia's research elucidated the impact of EWS on the formation of intestinal mucin O-glycans and the composition of intestinal microbiota, revealing that EWS led to the development of aberrant mucin O-glycans, characterized by truncated glycans, reduced acidic glycans, and elevated fucosyl glycans, which may contribute to intestinal inflammation and disease [53]. Additionally, EWS modified the gut microbial composition by increasing the prevalence of pathogenic bacteria, including E. coli and Shigella, further exacerbating risks to intestinal health.

Preoperative gut preparation

Preoperative gut preparation can significantly influence the diversity and functionality of the microbiota, which in turn affects postopera-

tive recovery. In a study by Wang et al. using 6-week-old MRL/lpr mice (a model for systemic lupus erythematosus), a notable reduction in the Firmicutes to Bacteroidetes ratio was observed [56]. This alteration in microbial composition was characterized by a decrease in the Peptostreptococcaceae family and an increase in the Rikenellaceae family, which were strongly correlated with heightened intestinal permeability in MRL/lpr mice, as indicated by elevated fecal levels of albumin and IgA, alongside reduced expression of the intestinal tight junction protein ZO-2. By 18 weeks of age, these mice exhibited signs of intestinal inflammation, including elevated levels of phosphorylated NF-κB, IL-6, and IgG in the colon, signifying an active inflammatory response in the gastrointestinal tract. Furthermore, a substantial increase in eubacterial populations was observed in the liver, suggesting that gut microbiota may have translocated to the liver via a compromised intestinal barrier, potentially initiating or exacerbating the hepatic immune response.

Immunosuppression

Preoperative immune status significantly impacts postoperative recovery. A study by Fragiadakis et al. highlighted the pivotal role of CD14+ monocytes in this process, demonstrating that their signaling responses, including pSTAT3, pCREB, and pNFκB, are closely linked with postoperative fatigue, hip function recovery, and pain alleviation [57]. Furthermore, the responses of classical and plasmacytoid dendritic cells to LPS and IL-2/GM-CSF stimulation were also correlated with postoperative recovery metrics. The study also highlighted that the Toll-like receptor 4 signaling pathway in monocytes is crucial for clinical recovery and emphasized that damage-associated molecular patterns (DAMPs), including high mobility group protein B1 (HMGB1) and heat shock proteins, activate innate immune cells via Toll-like receptor 4 receptors, significantly impacting postoperative recovery.

In addition, the preoperative immune status is closely linked to the risk of postoperative infection. The study by Zhang et al. demonstrated that patients who received transfusions exhibited significantly lower levels of TNF and IL-17A compared to those who did not receive transfusions, indicating a possible connection between the preoperative immune response and postoperative infection risk [58]. There was also a direct correlation between the robustness of the postoperative immune response and susceptibility to postoperative infection, as evidenced by postoperative immunosuppression. Torrance's study demonstrated a four-fold increase in IL-10 mRNA and protein levels following surgery, peaking within two hours post-surgery [59]. This was accompanied by a reduced expression of mHLA-DR on the cell surface, indicating postoperative immunosuppression. Elevated postoperative IL-10 levels are correlated with an increased risk of infection, suggesting that monocyte dysfunction and immunosuppression are common after major surgical procedures. Fortunately, clinically available immune stimulants, such as GM-CSF and interferon-gamma, have been shown to restore mHLA-DR levels, which may help reverse postoperative immunosuppression [59].

Period of operation

Surgical wound

Blunt abdominal trauma can result in early morphological damage to the intestines, particularly affecting the intestinal epithelial cells [60]. The extent of injury is directly proportional to the trauma's intensity; more severe trauma correlates with more pronounced intestinal damage, including manifestations such as intestinal bleeding and tissue rupture. Furthermore, the functionality of the intestinal immunologic barrier may be significantly compromised, facilitating to the translocation of intracellular molecules, such as intestinal fatty acid-binding protein, into the bloodstream. This translocation serves as a biomarker for intestinal barrier dysfunction, with its concentration being indicative of the trauma's severity.

Following trauma, the gastrointestinal tract triggers both local and systemic immune responses [61]. Neutrophils, serving as the primary line of defense, rapidly accumulate and become activated at the site of injury. This is accompanied by elevated plasma levels of inflammatory cytokines. These neutrophils migrate to the site of injury via chemotaxis, a process modulated by pro-inflammatory cytokines like IL-6 [61]. DAMPs released post-surgery, such as HMGB1, stimulate the formation of neutrophil extracellular traps through specific signaling pathways, thereby intensifying the inflammatory response [62]. Furthermore, systemic immune responses are characterized by increased plasma concentrations of inflammatory cytokines, such as macrophage inflammatory protein 2 and TNF [62]. While these immune responses help clear dead tissue and promote repair, they can also result in excessive inflammation, contributing to further tissue damage [60].

Traumatic injury can simultaneously trigger

both the SIRS and Compensatory Anti-inflammatory Response Syndrome [63]. These syndromes are induced by tissue damage and hemorrhagic shock, leading to the release of DAMPs from necrotic and injured cells. DAMPs activate immune cells and complement pathways through the engagement of pattern recognition receptors, initiating the release of cytokines involved in systemic inflammation [62]. HMGB1, a critical DAMP, is markedly elevated in the bloodstream following trauma and is correlated with injury severity, the onset of sepsis, and the development of MODS [63, 64]. Furthermore, HMGB1 exerts a direct influence on the vascular endothelium by facilitating neutrophil adhesion, enhancing endothelial permeability, and enhancing the production of adhesion molecules and cytokines [64].

Following trauma, the concentrations of pro-inflammatory cytokines and chemokines, including IL-1B, IL-6, IL-8, granulocyte-colony stimulating factor, and TNF-α, rise rapidly and remain elevated over hours and days [65]. Concurrently, the levels of various anti-inflammatory mediators, such as TGF-β1 and IL-10, also increase in circulation [66]. Patients with MODS show elevated levels of both pro-inflammatory and anti-inflammatory cytokines upon admission, in contrast to patients without MODS [66]. Furthermore, traumatic injury can alter neutrophil function and phenotype, alongside variations in lymphocyte counts, potentially increasing the risk of infections in trauma patients [67, 68]. Severely injured individuals often exhibit low levels of CD62L and high levels of CD11b on their cell surfaces, indicating neutrophil activation [67]. Furthermore, lymphocyte counts increases during the hyperacute phase (less than 2 hours) following injury, but significant lymphocytopenia can occur as early as 4 hours post-injury [68].

Anesthetic drug

Anesthetic agents have been shown to modulate innate immune responses by diminishing the cytotoxic activity of natural killer (NK) cells [69]. The underlying mechanism is likely multifactorial, with substantial evidence indicating the involvement of interferons [70]. Combined in vivo and in vitro studies in mice have demonstrated that anesthetic exposure inhibits interferon's ability to enhance NK cell toxicity, and this inhibitory effect can persist for several days post-anesthesia [70]. Clinical investigations further support these findings, showing a reduction in basal NK cell activity within the peripheral blood mononuclear cells of patients subjected to general anesthesia [71]. However, this diminished NK cell activity can be restored by interferon treatment [71]. Recent research indicates that sevoflurane and isoflurane cause a dose-dependent decrease in NK cell cytotoxicity, likely through inhibition of lymphocyte function-associated antigen 1, an adhesion molecule essential for NK cell functionality [72]. These findings may hold significant implications for oncological surgeries, considering the critical role of NK cells in cancer immune surveillance and immunoediting [73].

Anesthetic agents such as isoflurane and sevoflurane are known to suppress T lymphocyte function [74-76]. These anesthetics exert their inhibitory effects on T lymphocytes by impeding the transcription factor activating protein 1 and its downstream target gene IL-3 [74]. Additionally, isoflurane and sevoflurane induce apoptosis in T lymphocytes in a dose-dependent manner, and also influence production of B lymphocytes and cytokines [75]. Specifically, isoflurane and sevoflurane inhibit the secretion of pro-inflammatory cytokines, including IL-1β and TNF-α, from human peripheral monocytes in response to tumor cells, which may potentially facilitate tumorigenesis [76].

Hypoxia

Hypoxia is a crucial physiological phenomenon within the intestine, exerting significant effects on both physiological and pathological states of the body [77]. Within intestinal tissue, a pronounced vertical oxygen gradient is established between the submucosa, which is abundant in blood vessels, and the nearly anoxic intestinal lumen [78]. In the colonic region, the partial pressure of oxygen progressively declines from approximately 145 mmHg (around 21% O_2) to markedly low levels within the intestinal lumen [79]. A similar gradient exists in the small intestine, albeit with differing specific values [79].

The adaptation of intestinal cells to hypoxic conditions is primarily governed by hypoxia-inducible factors [80]. Under hypoxic conditions, hypoxia-inducible factors become stabilized and facilitates the expression of a series of genes that enable cellular adaptation to low-oxygen environments. These genes predominantly include erythropoietin (regulating erythropoiesis), vascular endothelial growth factor (promoting angiogenesis), and glycolytic enzymes (modulating cellular metabolism) [81, 82]. Furthermore, research has demonstrated that acute hypoxia, such as that induced by surgical procedures, can compromise the integrity of the intestinal barrier [83]. Brief exposure to hypoxia leads to elevated secretion of IgA

and pro-inflammatory cytokines, alongside enhanced expression of pro-inflammatory markers like Toll-like receptor 4 and inducible nitric oxide synthase (iNOS) [83]. Prolonged hypoxia leads to a marked increase in the populations of IL-17-producing cells, NK cells, and dendritic cells within the gut, while significantly reducing the number of naive T cells in Peyer's patches [83]. These findings underscore the complex influence of hypoxia on intestinal immune function.

Ischemia reperfusion

Ischemia-reperfusion (I/R) injury is a common pathological condition that triggers a systemic inflammatory response, resulting in damage to multiple organs and potential functional failure. Research has demonstrated that miR-185-5p is upregulated in I/R conditions, exacerbating intestinal barrier damage by inhibiting the autophagy pathway [84]; ATG101 has been identified as a target gene of miR-185-5p, and its overexpression can enhance autophagy, thereby mitigating the intestinal barrier damage induced by I/R [84]. Intestinal I/R injury can induce stress and damage to IECs, potentially leading to their death and mitochondrial dysfunction. This dysfunction results in elevated levels of mitochondrial DNA (mtDNA), with plasma mtDNA serving as a predictor for SIRS risk following trauma [84, 85]. The release of mtDNA due to intestinal I/R injury can activate resident immune cells, thereby enhancing the production of inflammatory cytokines within the gut [84]. Zhang et al. have demonstrated that mtDNA can cause neutrophil-mediated organ damage, which is associated with increased secretion of TNF-α and IL-6 [85]. Numerous studies have indicated that the Toll-like receptor 9-MyD88 signaling pathway plays a role in intestinal I/R injury [86]. For instance, Victoni et al. demonstrated that the absence of MyD88 resulted in reduced intestinal inflammation and injury, which is linked to diminished neutrophil recruitment and decreased production of pro-inflammatory cytokines [86]. Furthermore, prior study has shown that the administration of oxidized mtDNA via tail vein injection enhance the levels of inflammatory mediators and chemokines [87].

Perioperative complications and intestinal immunologic barrier

Infection

Dysfunction of the intestinal immunologic barrier constitutes a significant contributor to postoperative infections [59]. Surgical site infections, in particular, represent the predominant cause of hospital readmissions, thereby escalating healthcare expenditures [5].

Despite efforts to target environmental and skin-derived microorganisms, approximately 10% of patients still experience postoperative infections [88]. A clinical analysis of 3,515 patients who developed infections after general surgical procedures revealed that the primary pathogens were common intestinal microorganisms, such as *Escherichia coli*, and *Clostridium sp.*, suggesting that these pathogens may have breached the intestinal barrier and entered the systemic circulation [88]. Furthermore, numerous studies have demonstrated that perioperative probiotic therapy for patients undergoing colorectal cancer surgery can improve intestinal microecology and enhance immune responses, resulting in a significant reduction in superficial incisional infection rates postoperatively [89-92].

Anastomotic leakage

Infection and other factors contribute to impaired anastomotic healing and the formation of fistulas. Anastomotic leakage represents one of the most potentially severe complications that can arise during the reconstruction of the digestive tract following major surgical procedures, posing a significant challenge for surgeons [5]. A critical aspect of normal wound healing is the development of granulation tissue, which includes fibroblasts, collagen, and blood vessels, signaling a healing response [93]. Postoperative bacterial infection at the anastomotic site can exacerbate inflammation and hinder this healing process [5].

Dysbiosis of the intestinal microbiota has been recognized as contributor to anastomotic leakage [94]. Several clinical studies have shown that perioperative oral antibiotic therapy (or local decontamination) in patients undergoing gastrointestinal surgery can significantly reduce the incidence of anastomotic leakage [95-98]. Some intestinal bacteria are known to produce collagenases that degrade collagen in the intestinal wall and stimulate intestinal epithelial cells to secrete matrix metalloproteinases 9, exacerbating tissue damage and local inflammation. This mechanism may explain how intestinal pathogens promote anastomotic leakage. The microbial composition in biological samples (such as feces, mucosa, the resected specimen, or drain fluid) from patients with and without anastomotic leakage after colorectal surgery were compared, and the findings indicated that collagenase-producing bacteria are more

common in patients with anastomotic leakage, such as *Fusobacterium nucleatum* [99-100]. Serial animal experiments have also confirmed that local colonization with collagenase-producing bacteria (such as *Enterococcus faecalis* and *Pseudomonas aeruginosa*) can increase the incidence of postoperative anastomotic leakage, while administration of plasminogen inhibitors to mice postoperatively can effectively alleviate collagen degradation and colonic perforation [101-102].

SIRS

The translocation of bacteria and endotoxins resulting from compromised intestinal barrier integrity can trigger systemic inflammatory responses. Infections, characterized by the invasion of pathogens such as bacteria, viruses, and fungi, represent a primary cause of SIRS [5]. These pathogens activate the host's immune system, eliciting an inflammatory response [2]. Aberrant secretion of inflammatory mediators can weaken the tight junctions between intestinal epithelial cells, increasing intestinal permeability and facilitating the translocation of intestinal bacteria and endotoxins into the systemic circulation [33]. This impairment of the intestinal immunologic barrier exacerbates the systemic inflammatory response, creating a deleterious cycle. Once bacteria and endotoxins enter the systemic circulation, they elicit an amplified immune response and inflammatory cascade, potentially resulting in tissue and organ damage. Furthermore, impairment of the intestinal immunologic barrier may initiate inflammation and contribute to the development of autoimmune diseases within the gastrointestinal tract.

In a study comprising 85 patients diagnosed with SIRS, a positive correlation was identified between gut bacterial load and blood levels of IL-6 [103]. This observation suggests that compromised intestinal barrier integrity may facilitate bacterial translocation into the bloodstream, thereby initiating systemic inflammatory responses. Additionally, elevated levels of intestinal fatty acid-binding protein were significantly associated with hypotension, increased respiratory rate, hyperglycemia, and elevated Sequential Organ Failure Assessment scores. These findings further substantiate the direct relationship between intestinal epithelial damage and the severity of SIRS.

Conversely, pediatric multi-system inflammatory syndrome, characterized by systemic inflammation and multiple-organ involvement, may be linked to disruptions in the IL-6 signaling pathway induced by the SARS-CoV-2 virus [104]. Recent research has identified an intrinsic connection between intestinal barrier integrity and IL-6 levels, suggesting that the bacteriophage-like properties of SARS-CoV-2 might enhance interactions between the virus and gut microbiota [104]. This interaction could lead to increased translocation of viral components and bacterial toxins, thereby exacerbating systemic inflammation [104].

Gastrointestinal motility disorder

Gastrointestinal dyskinesia is a common consequence of significant gastrointestinal remodeling, encompassing conditions ranging from malabsorption (linked to increased gastrointestinal motility) to postoperative intestinal obstruction (POI) [105]. Intestinal immune cells are crucial in regulating gastrointestinal physiology, particularly in terms of motility. POI refers to the temporary cessation of coordinated gastrointestinal motility following abdominal surgery, which adversely affects quality of life, extends hospital stays, and escalates socioeconomic costs [105].

Alterations in the gut microbiota following gastrointestinal surgery largely contribute to changes in gastrointestinal motility [106]. In the POI model, notable alterations in the microbial community were observed, including a reduction in the abundance of *Lactobacillus* (including both *Bifidobacterium* and *Lactobacillus*) and an increase in *Bacteroides* and *Blautia* [107]. Another clinical study showed that patients with colorectal cancer who have a lower abundance of Faecalibacterium are at a higher risk of developing postoperative intestinal obstruction [108]. A meta-analysis involving 1,773 subjects confirmed that perioperative supplementation with probiotics or synbiotics can effectively promote gastrointestinal function recovery after gastrointestinal cancer surgery [109]. These microbial shifts were also associated with decreased fecal butyrate levels [107]. Butyrate, a crucial short-chain fatty acids (SCFAs), serves as the primary energy source for intestinal epithelial cells and is critical for enhancing intestinal barrier function [107].

Additionally, butyrate plays a central role in immune regulation, notably by promoting the differentiation of colonic regulatory T cells to help suppress inflammatory responses [107]. Further research by Parada Venegas et al. demonstrated a significant reduction in butyrate-producing bacteria, which is closely linked to a decrease in fecal SCFAs [110]. While the precise mechanism linking reduced SCFAs to

heightened immune activation and increased permeability is yet to be fully elucidated, probiotic treatment has demonstrated efficacy in restoring SCFAs levels, particularly in malnourished individuals. Probiotics also enhance the expression of G-protein-coupled receptors, including GPR41, GPR43, and GPR109A, on macrophages [110]. The interaction of SCFAs with these receptors facilitates the repair of epithelial barrier function and the activation of anti-inflammatory signaling pathways.

Improving gut barrier may reduce postoperative complications

Liver transplantation is the only effective treatment for end-stage liver diseases, yet postoperative infections significantly reduce the surgery's success rate. Gut barrier dysfunction is a primary cause of early postoperative infectious complications following liver transplantation. Bacterial translocation disrupts the intestinal barrier, enabling pathogens to enter the bloodstream and trigger infections [111]. Clinical trials have shown that the combination therapy of probiotics/prebiotics can significantly reduce the incidence of postoperative bacterial infections, thus leading to shorter hospital stay or antibiotic therapy [112]. For postoperative colorectal cancer patients, probiotics had been proven to effectively reduce infectious complications by improving the integrity of the gut mucosal barrier [113]. In the case of anastomotic leak, animal experiments have demonstrated that exogenous butyrate administration enhanced the healing and strength of colonic anastomoses in rats [114]. Furthermore, supplementation with probiotics or synbiotics during the peri-operative period may improve gastrointestinal motility recovery following gastrointestinal surgery. A recent meta-analysis by Tang et al. indicated that peri-operative probiotics or synbiotics supplementation effectively shortened the time to first flatus and first defecation, while also reducing POI [115].

Conclusion

This review provides a comprehensive summary of the role of intestinal barrier dysfunction in perioperative complications, emphasizing the significant impact of immunologic barrier damage on postoperative outcomes. A close interaction exists between the intestinal immunologic barrier and the intestinal microbiome, wherein intestinal epithelial cells and immune cells detect microorganisms via pathogen recognition receptors. Concurrently, microbial metabolites, such as short-chain fatty acids, exert regulatory effects on intestinal immune cells. Under healthy conditions, a homeostatic balance is maintained between microbial populations and immune cells. Disruption of this equilibrium triggers an immune response. The intestinal epithelium serves as the primary defense mechanism, forming a barrier through the tight junctions and secretory cells, including goblet cells and Paneth cells. Concurrently, pro-inflammatory cytokines, such as TNF-α, IL-13, and IL-6, play key roles in modulating intestinal tight junctions and maintaining barrier integrity.

Preoperative factors, including malnutrition, stress response, intestinal readiness, and immunosuppressive status, alongside operative factors such as surgical trauma, anesthetic agents, hypoxia, and ischemia-reperfusion, can undermine the integrity of the intestinal immunologic barrier. This, in turn, increases the risk of postoperative complications, such as infection, anastomotic leakage, systemic inflammatory response syndrome, and gastrointestinal motility disorders.

The innovation of this review lies in its comprehensive analysis of the specific mechanisms through which the intestinal immunologic barrier contributes to perioperative complications. It highlights the necessity for further investigation into the interaction between the intestinal microbiota and the immunologic barrier to enhance perioperative management strategies.

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