

Intestinal Mucosal Immune Barrier: A Powerful Firewall Against Severe Acute Pancreatitis-Associated Acute Lung Injury via the Gut-Lung Axis

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Abstract: The pathogenesis of severe acute pancreatitis-associated acute lung injury (SAP-ALI), which is the leading cause of mortality among hospitalized patients in the intensive care unit, remains incompletely elucidated. The intestinal mucosal immune barrier is a crucial component of the intestinal epithelial barrier, and its aberrant activation contributes to the induction of sustained pro-inflammatory immune responses, paradoxical intercellular communication, and bacterial translocation. In this review, we firstly provide a comprehensive overview of the composition of the intestinal mucosal immune barrier and its pivotal roles in the pathogenesis of SAP-ALI. Secondly, the mechanisms of its crosstalk with gut microbiota, which is called gut-lung axis, and its effect on SAP-ALI were summarized. Finally, a number of drugs that could enhance the intestinal mucosal immune barrier and exhibit potential anti-SAP-ALI activities were presented, including probiotics, glutamine, enteral nutrition, and traditional Chinese medicine (TCM). The aim is to offer a theoretical framework based on the perspective of the intestinal mucosal immune barrier to protect against SAP-ALI.

Keywords: severe acute pancreatitis-associated acute lung injury, intestinal mucosal immune barrier, gut microbiota, gut-lung axis, migration of immune cells

Introduction

Severe acute pancreatitis (SAP) is one of the most common abdominal critical emergencies in clinical practice. According to the 2012 Revision of the Atlanta Classification Standard (RAC) by the International AP Consensus and the 2014 Guidelines for diagnosis and treatment of the acute pancreatitis guide by the Chinese medical association branch, SAP is defined as acute inflammation of pancreas, and its main manifestations include pancreatic edema, necrosis, hemorrhage, infection, peripancreatic fluid collection, wall necrosis (WON), and extrapancreatic organ dysfunction or failure.^{1,2} The main cause is the destruction of pancreatic acinar cells and bile duct cells, leading to the activation of trypsin and lipase in pancreatic tissue.^{3,4} And it is often accompanied by organ failure lasting for more than 48 hours. The pathological process is characterized by an aggressive nature and the potential involvement of one or multiple organs, resulting in a mortality rate of up to 35%.^{5,6} The incidence of SAP has increased in recent years, with an estimated number of 110 to 140 cases per 100,000 population.^{4,7-9} Acute lung injury is one of the most serious and earliest complications secondary to SAP, which usually manifests as a decrease in alveolar surface-active substances, an elevation in oxygen-free radicals and permeability of alveolar epithelial cells, accumulation of inflammatory proteins, and injury to the endothelial cells of the pulmonary microvasculature. This accounts for 70% of the mortality rate among patients with SAP.¹⁰⁻¹² The occurrence of SAP-ALI is

typically accompanied by the release of inflammatory mediators in a cascading manner, disruption of the intestinal barrier function, imbalance of immune systems, as well as alterations in intestinal bacteria and their pathogen-associated molecular patterns (PAMPs).^{13–16} SAP-ALI as a typical complication of SAP, is the main cause of death in SAP patients, and its mortality rate is more than 30%.^{17–23} The current focus of SAP-ALI research is to find ways to reduce the inflammatory response and the expression of inflammatory factors.^{24,25} Endotoxemia, systemic inflammatory response syndrome and multiple-organ failure are common complications in the development of SAP.²⁶ In SAP, the levels of proinflammatory cytokines TNF- α , IL-6, and IL-1 β are elevated, and neutrophils and pancreatic enzymes are key indicators of inflammatory response.²⁷ Pro-inflammatory cytokines enter the intestine through microcirculation, damage the mucosa and destroy the intestinal barrier, which is an important factor affecting the course of SAP-ALI.^{28,29} However, the exact mechanisms of action and regulatory targets remain to be fully elucidated.^{30–32}

The intestinal mucosal immune barrier is the primary site for the initiation and activation of the immune response, exerting influence on the integrity of the intestinal barrier and attenuation of the systemic inflammatory response. It also plays a crucial role in maintaining intestinal immune homeostasis, and regulating the long-range migration of immune cells along the gut-lung axis.^{33,34} In addition, crosstalks between the gut microbiota or its derived small molecules and intestinal immune cells are important in the maintenance of a favorable immune microenvironment and facilitating bi-directional communications among intestinal cells, ultimately influencing the integrity of the intestinal barrier.^{35–37} Current studies have shown that the intestinal mucosal immune barrier actively contributes to the protection against SAP-ALI, and any disruption to this barrier can expedite disease progression and impact the prognosis of patients.^{38,39}

Currently, there is a lack of reviews regarding the role of the intestinal mucosal immune barrier in the pathogenesis of SAP-ALI. In this paper, we provide a detailed account of the composition and potential mechanisms of the intestinal mucosal immune barrier in SAP-ALI. Additionally, we investigate the relationships between the intestinal mucosal immune barrier and gut microbiota via the gut-lung axis to enhance our understanding of bacterial translocation and immune cell migration in SAP. Finally, we summarize several drugs that could strengthen the intestinal mucosal immune barrier, which is prospective to provide new sights to be utilized in SAP-ALI patients in the future.

Composition of the Intestinal Mucosal Immune Barrier

The intestinal mucosal immune barrier is mainly composed of intestinal epithelial cells (IECs), gut-associated lymphoid tissue (GALT), immune cells (macrophages, antigen-presenting cells, monocytes, neutrophils, etc.), the secretion of plasma cells produce secretory IgA (SIgA), and immune active substances (antibodies, cytokines, lysozyme, defensive element).^{40,41} The intestinal mucosal immune barrier plays an important role in defending against bacterial, viral or toxin invasions, as well as regulation in anti-allergic reactions, and suppression of sustained pro-inflammatory immune responses.⁴² The intestinal mucosal immune barrier, an important component of the host immune system, plays a crucial role in resisting pathogen translocation, stabilizing the immune microenvironment, attenuating systemic inflammatory responses and regulating the bidirectional communications between the immune cells.

Intestinal Epithelial Cells (IECs)

IECs are the initial cells that contact with the gut microbiome and actively contribute to the immune response of the gastrointestinal tract. It is mainly composed of the intestinal stem cells (ISCs) located in Lieberkühn crypts (marked by Lgr5, leucine-rich repeat-containing G protein-coupled receptor 5) and its differentiated cell lineage including intestinal absorptive epithelial cells (IAECs), goblet cells (GCs), microfold cells (M cells), Paneth cells (PCs) and enteroendocrine cells (EEs).^{43–45} The intestinal form of the natural physical barrier is composed of the IECs cortex, which separates immune cells in the lamina propria from the lumen and facilitates two-way communication between them and the symbiotic anaerobic bacteria for immune tolerance.⁴⁶ IECs stimulated by microbiota and IFN- γ promote the differentiation of CD4⁺ CD8 $\alpha\alpha$ ⁺ IELs by expressing MHC class II (MHC II) and programmed death ligand-1 (PD-L1).⁴⁷ In addition, IECs receive signals via herpes virus entry mediator (HVEM) on their surface and stimulate the synthesis of basement membrane proteins, and they interact with adhesion molecules expressed on the surface of T cells, called integrins, to perform immune patrolling and surveillance functions.⁴⁸ Endoplasmic reticulum stress in IECs promotes the expression of Duoxa2/Duox2, leading to the increase in reactive oxygen species (ROS). Enhanced ROS signals could

activate purine metabolic pathways, which in turn lead to an increased release of xanthine from IECs, ultimately inducing the differentiation of Th17 cells, and it may be an important source of the inflammatory storm triggered during SAP.^{49,50}

Leucine-Rich Repeat-Containing G Protein-Coupled Receptor 5 Positive Intestinal Stem Cells (Lgr5⁺ ISCs)

IECs possess a rapid capacity for renewal and repairment (3–5 days renewal).⁵¹ As the initial source of various types of intestinal cells, ISCs provide the neoplastic force to keep the intestines always fresh and alive.⁵² Lgr5 acts as an important molecule for tracking ISCs in vivo as an ISC-specific marker.⁵³ Human Lgr5 ISCs are predominantly p27-positive cells that occupy ecological niches at the base of crypts, thereby preventing the dedifferentiation of differentiated cells.⁵⁴ ISCs are located at the basal part of the intestinal raised villous crypts and are arranged in interspersed rows with PCs. Transit amplifying cells (TACs), generated by ISCs, gradually migrate from the bottom of the crypts to the top of the crypts and differentiate into a variety of intestinal cells.⁵⁵ TACs firstly give rise to the secretory and absorptive progenitors, which subsequently differentiate into mature GCs, EEs, and PCs, and absorptive progenitors differentiate into IAECs.^{56,57} The differentiated mature cells eventually migrate to the tip of the villi and undergo gradual apoptosis, subsequently being replaced by newly migrated cells from below.⁵⁸ ISCs are capable of plasticity, and in the event of acute injury resulting in the loss of Lgr5⁺ ISCs, the intestine triggers a regenerative response to restore self-renewal capacity to compensate for the lost number in cell numbers.⁵⁹ The behavior of ISCs is influenced by the basolateral microenvironment, which consists of gut bacteria, signaling pathway-associated ligands, soluble cytokines, chemokines and growth factors.^{59–62} Lymphatic endothelial cells (LECs) and fibroblasts (RSPO3⁺ GREM1⁺ fibroblasts, RGFs) in the ISCs microenvironment are the main cellular sources of the key ISC microenvironmental factor RSPO3, which has a major impact on the behavior of ISCs under intestinal homeostasis and the regeneration of intestinal epithelial performs a supportive role for ISCs.⁶³ Current studies have shown that the reduction of Lgr5⁺ ISCs in response to intestinal injury is accompanied by the increased secretion of stem cell factors and the enhanced ISCs functions, which is associated with the re-entry of PCs into the cell cycle, the loss of the secretory phenotype, and the acquisition of stem cell properties, which contribute to the regeneration of tissues and the response to the inflammation.^{64,65} The interaction between ISCs and the immune cells represents a promising therapeutic target in the context of SAP-ALI.⁶⁶

Goblet Cells (GCs)

GCs, a special type of epithelial cell dispersed among IAECs, perform innate immune functions by the secretion of mucus and the production of mucin, chemokines and cytokines. The numbers gradually increase from the duodenum to the end of the ileum.^{67–69} The formation of goblet cell-associated antigen passages (GAPs) enables GCs to prevent bacterial invasion into the intestinal mucosa and facilitate the transmission of post-feeding protein and antigen signals to the dendritic cells, thereby promoting the development of tolerance.^{70–72} Alterations in the microenvironment of the mucus system that are caused by dysfunctional GCs or the lack in specific types of GCs can accelerate the process of the inflammatory responses and increase the fixed resistance against pathogenic microorganisms.^{73,74} In addition, mucus secretion by GCs and mucus layer thickness could be regulated by autophagy and endoplasmic reticulum stress could be attenuated in a bacterial- and Nod2-dependent manner.^{75,76} As an important factor of intestinal mucus barrier damage in SAP-ALI, its causal relationships with the gut microbiota, the feedback mechanisms in immune responses, and the targets for GCs' differentiation in SAP are still the current focus of basic research.^{77–79}

Paneth Cells (PCs)

PCs are a type of specialized secretory cells that differentiate at the base of the crypt, and their maintenance requires the secretory regulatory protein Atoh1, a downstream target of Wnt/b-catenin signaling for innate immune functions.⁸⁰ Upon signals from bacteria in the intestinal mucus layer alter, PCs secrete antimicrobial substances such as antimicrobial peptides (AMPs), defensins, and lysozymes into the mucus layer to protect the intestinal barrier.^{81,82} PCs have a unique ecological niche, which facilitates their interactions with ISCs and protects ISCs from changes in the intestinal microenvironment.⁸³ In addition, the PI3K/AKT/mTOR signaling axis mediated by IL-22 (activated upon SAP) is involved in the differentiation of PCs and influences the expression of intracellular host defense genes (REG1A, REG1B, DMBT1).^{84–86} Despite the similar number and distribution of LGR5⁺ ISCs in the small and large intestinal crypts, the number of effective stem cells (capable of forming long-lasting cell clones) in the small intestinal crypts was

two times higher than that in the large intestine due to the motility of retrograde cells that is dependent on Wnt signaling.⁸⁷ In addition, loss of the functions and mutation of PTPN2, a key regulator to maintain the vitality and functions of PCs, could accelerate the expansion of inflammatory response.^{65,88} In summary, the intestinal tract is not as active as it should be in SAP. The weakness of the intestinal mucus layer, the reduced secretion of AMPs, and the increased abundance of pathogenic bacteria in SAP are closely related to the impaired function of PCs.^{40,89}

Microfold Cells (M Cells)

M cells are key cells in intestinal immunity, characterized by short, few, irregular villi and special micro folds, and are known as the zone where antigens can cross in the host intestinal mucosa.⁹⁰ Although M cells are not involved in the digestion and absorption, they could selectively capture or transfer antigens to the lamina propria of the mucosa, allowing antigens to be acquired by DCs and then recognized by immune cells to elicit specific immune responses.^{91,92} As the sentinel cells, the abundance of M cells can be modulated by gastrointestinal injury-sensing neurons and exert resistant effects against pathogenic bacteria through releasing calcitonin gene-related peptide (CGRP).⁹³ The transcription factor ONECUT2 is activated in response to pancreatic alveolar cell damage and acts as a downstream of RANK/RANKL, which supports the differentiation of IEC and inhibits M-cell lineage specialization, thereby indirectly regulating functions of B cells and production of SIgA.^{94,95} NADPH oxidase-1 (NOX1), which is involved in the production of ROS, is significantly up-regulated during SAP, and the differentiation and plastination of M-cells are inhibited, which in turn affects the course of the adaptive immune response.^{96,97} In addition, present on M cells is capable of recognizing and internalizing β -glucan-rich probiotics, thereby eliciting an immune response in the intestinal mucosa, emerging as a feasible strategy for the modulation of immunity by regulation in gut microbiota.⁹⁸

Enteroendocrine Cells (EECs)

EECs are distributed throughout the intestinal epithelium, accounting for merely 1% of total intestinal cells. They possess a high sensitivity to chemical cues such as luminal food stimuli and pH fluctuations, thereby exerting regulatory effects on intestinal functions, systemic metabolism, and food intake through hormone secretion.^{99,100} As the largest endocrine system in the human body, the gut microbes and their metabolites (SCFAs, secondary bile acids, LPS, etc.) are effective stimulators of EECs, which could produce hormonal signals via G-protein coupled receptors, nutrient transporter proteins and ion channels.¹⁰¹ It has been shown that bacteria in gut could influence the protein modification of O-GlcNAc by increasing the synthesis of SCFAs and regulating the differentiation of intestinal endocrine L-cells to enhance the energy metabolism of IECs, which in turn indirectly enhances the intestinal barrier.¹⁰² The necrotic apoptosis of IECs may be closely related to the function of EEs in SAP.¹⁰³ Apart from this, tryptophan derivatives produced by intestinal bacteria could activate Trpa1 channels on EEs, leading to a rapid activation of the intestinal vagus nerve, resulting in an increase in intestinal peristalsis and a faster rate of substance absorption in SAP.^{104,105} Enterochromaffin cells, as a type of rare excitatory EECs, are capable of recognizing stimulations and acting on the intestinal innervating afferent nerves to release 5-hydroxytryptamine, thereby transmitting nociceptive signals to the spinal cord, which is involved in the immunomodulation effects in the intestine.¹⁰⁶ Although EEs indirectly influence intestinal mucosal immunity, they are essential for the energetic input of IECs and their communication with immune cells.

Gut-Associated Lymphoid Tissue (GALT)

GALT mainly consists of Peyer's patch (PP), intestinal intraepithelial lymphocytes (IELs), lamina propria lymphocytes (LPLs), lymphoid follicles and mesenteric lymph nodes (MLNs).¹⁰⁷ The distribution of immune cells and GALT shows a regional pattern along the intestinal mucosal layers and intestinal canal walls.¹⁰⁸

Peyer's Patch (PP)

PP consists of hundreds of lymphoid follicles surrounded by follicle-associated epithelium containing M cells and is predominantly found in the distal ileum.¹⁰⁹ The PP is an important lymphoid organ for bacterial colonization and activation of T cell-dependent IgA signals.^{110,111} Bacteria clustered on the surface of the PP are predominantly *Serratia* and *Lactobacillus spp*, while, those clustered inside the PP are mainly *Alkalobacter spp* and *Pallobacterium spp*.¹¹² An important function of PP is the uptake and monitoring of intestinal antigens (including bacteria), and activation of immune cells within PP may be involved in the

limitation of bacterial translocation.¹¹³ Entry of bacteria into the PP triggers sustained pro-inflammatory immunity, and disruption of the intestinal flora within the PP could cause a severe inflammatory response, resulting in damage to intestinal mucosa on the surface of PP and induction of excessive bacterial invasion.¹¹⁴ Fibroblasts in PP are considered the ecological niche-supporting cells in epithelial crypts, the coordinators of lymphoid tissue and mediators of stromal-immune interactions.¹¹⁵ Innate lymphoid cells (ILCs) in PP could induce the expression of the antimicrobial proteins (RegIII β and RegIII γ in IECs) and maintain homeostasis in gut microbiota by regulating IL-22 and IFN- γ signals.¹¹⁶ PP-derived mesenchymal stromal cells (MSCs) perform enhanced immunomodulatory capacities and inhibit the abnormal proliferation of T-cells as well as the production of inflammatory factors.¹¹⁷ Robo4 is also a regulator of the vascular endothelial barrier during pancreatic inflammation, which could induce the renewal and regeneration of B-cells in PPs,^{118,119} while, subsequent transcriptomics data are needed in terms of SAP-ALI.

Intraepithelial Lymphocytes (IELs)

IELs, a phenotypically heterogeneous population of T cells within the intestinal epithelium, dominate the defense of the mucosal immune system and are considered the frontline of immune surveillance by fending off pathogens and maintaining the epithelial integrity.^{120,121} The IELs can be classified into two primary cell subpopulations, the TCR $\gamma\delta^+$ T cells and TCR $\alpha\beta^+$ T cells.¹²² IELs are surrounded by IECs with a ratio of approximately 10:1 (IECs: IELs) in the ileum.¹²³ TCR $^+$ IELs express either TCR $\gamma\delta^+$ or TCR $\alpha\beta^+$, whereas the former is closely associated with the crosstalk with IECs and leads to more effective immune surveillance and higher expression of antimicrobial-associated genes.^{123,124} IELs are present at the outermost layer of the intestinal epithelial barrier and sense alterations in the intestinal microenvironment (eg, commensal anaerobes, PAMPs, toxins, or other small-molecules).¹²⁵ Activation of glucagon-like peptide-1 (GLP-1) in intestinal IELs is closely related to the composition of the gut microbiota and the inflammatory state on the intestinal epithelial surface.¹²⁶ The aryl-hydrocarbon receptor (AhR) is required for the maintenance of IELs and inhibition of AhR prevents lipid peroxidative stress and iron death in IELs.¹²⁷ It is reported that activation of AhR can reduce the AP-induced inflammation by inducing the expression of IL-22, suggesting that activation of IELs by AhR mediated may be a new direction to protect against SAP-ALI.¹²⁸

Lamina Proprial Lymphocytes (LPLs)

LPLs, diffusely distributed in the lamina propria of the mucosa, include CD4 $^+$ T cells, SIgA $^+$ B cells, NK cells, macrophages, mast cells, dendritic cells, and innate lymphoid cells (ILCs).^{129,130} T cells could secrete inflammatory cytokines such as IL-10 and TGF- β , and modulate the secretion of SIgA by B cells.¹³¹ The immune cells with a large amount in the lamina propria exert innate and adaptive immune functions through the transformation of information.¹³² The $\gamma\delta$ T cells in LPLs are capable of secreting IL-17 and perform similar functions with Th17 effector cells and ILCs.¹³³

The activation of ILCs, which include ILC1, ILC2, and ILC3 as well as NK cells, is independent of antigen-specific recognition and exhibits plasticity as they lack the expression of specific/pan-specific antigen receptors.^{134,135} ILCs are important in the anti-infected activities in mucosa and the maintenance of homeostasis in tissues.¹³⁶ The presence of ILC1 cells has been observed in both the small intestine and colon, where they actively secrete cytokines such as IFN- γ and TNF- α . These cells play a crucial role in maintaining the integrity of the intestinal mucosa by exerting potent anti-infective effects in response to microbial dysbiosis.¹³⁷ The activity of ILC2 is mediated by IL-4, IL-5, IL-9 and IL-13. This response is predominantly driven by IL-33, thereby promoting the hyperplasia of GCs, production of mucus, infiltration of eosinophils, and the fibrotic processes within tissues.¹³⁶ ILC3 maintains the intestinal barrier integrity as a patrol in the intestinal tract, and induces the expression of IL-22. In addition, altered migration patterns were observed in ILC3.¹³⁸ Despite the reduced number of NK cells in the early stage, the hyperreactive state of them is considered an important part of SAP, representing a systemic response of inflammation.¹³⁹ In short, ILCs exert complex and diverse roles in the polarization, homeostasis and apoptosis of macrophages, the network of which is a dominant factor in immune homeostasis.^{140,141}

Secretory IgA (SIgA)

SIgA serves as a primary effector of the immune system, being synthesized by plasma cells in the lamina propria and subsequently released onto the mucosal surface. SIgA is considered the first line of defense against the adhesion and colonization of pathogenic bacteria and the pioneer of mucosal immune protection.^{142,143} SIgA has multiple functions,

including forming antigen-antibody complexes to encapsulate bacteria, stimulating the secretion of intestinal mucus, preventing bacterial adherence, and neutralizing toxins.^{144–146} SIgA in gastrointestinal mucus directly affects the resistance to pathogens and the local immunity against infections, and a significant reduction in SIgA has been found in SAP.^{147,148} While, B-1 cell-specific protein (MZB1) is essential for maintaining the secretion of SIgA during acute enteritis.¹⁴⁹ The retrograde transport of SIgA-pathogen complexes into the GALT appears to be particularly crucial for initiating an adaptive immune response, which may necessitate the involvement of NOD2 as well as the Dectin-1 receptor.^{150,151} The remote modulation mechanisms and effectors of SIgA-bacterial complex after a damage in the intestinal mucosal immune barrier under SAP merits further investigations.

Other Immune-Related Active Substances

Other active substances secreted in the intestinal epithelium include defensins, Mucin2 (MUC2), and complements, which are involved in the immune responses during SAP-ALI. It has been reported that they are engaged in the clearance of pathogens or inflammatory mediators, and the activation of humoral and cellular immunity, etc.¹⁵² Defensins are mainly divided into two types, namely α -defensins and β -defensins.¹⁵³ α -defensins exhibit antimicrobial activities even after being degraded by intestinal proteases into fragments. β -defensins perform a strong structural plasticity, which can prevent the direct contact of the pathogenic microorganisms with IECs.¹⁵⁴ The expression of defensin is associated with the composition of SCFAs levels, which may involve mTOR and STAT3 pathways.¹⁵⁵ MUC2 provides the nutrients and shapes the composition and functions of the intestinal microbes and could maintain the intestinal immune homeostasis by actively regulating the production of AMPs, altering the activity of antigen-presenting cells, enhancing the clearance of bacteria as well as the immune cell communications.¹⁵⁶ The complement system comprises a collection of biologically active proteins that are found on the surface of the intestinal epithelium, capable of modulating immune responses and serves as a crucial component in maintaining the intestinal mucosa.^{157,158} It is expected that MUC2 and complements to be effective therapeutic targets for SAP-ALI (for details see Figure 1).

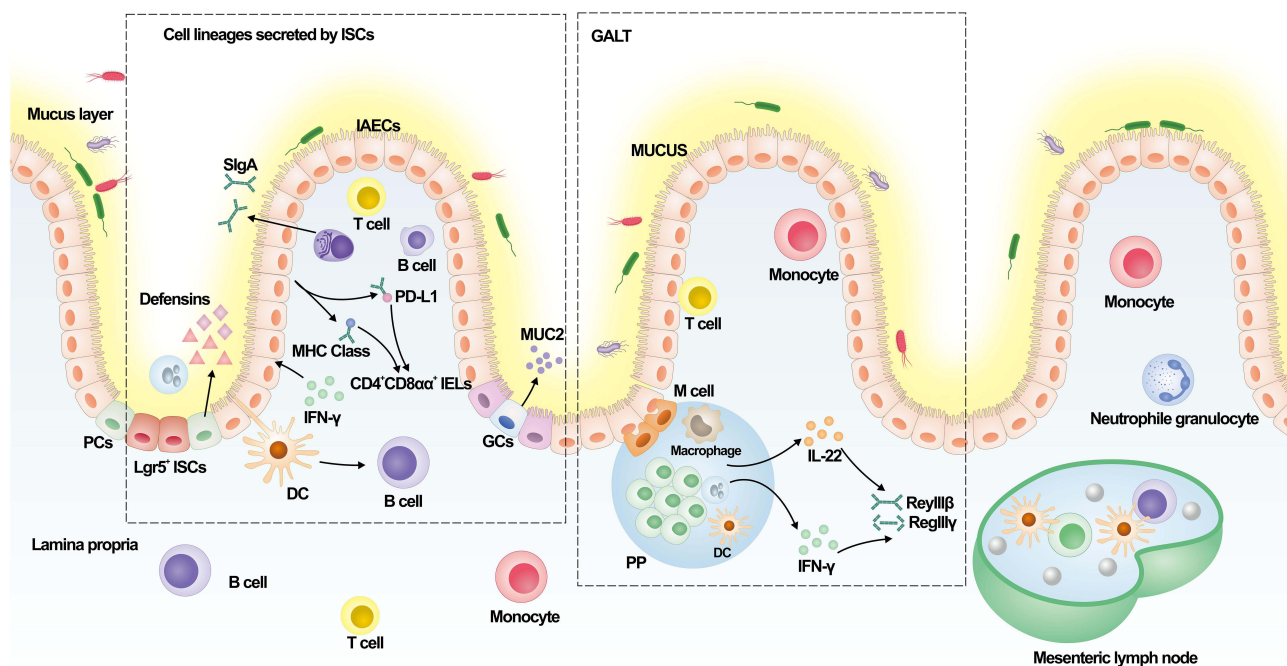


Figure 1 The composition of the intestinal mucosal immune barrier. The lineage originating from gut stem cells and gut-associated lymphoid tissues is primarily responsible for the intestinal immune responses; IECs express MHC, class II and PD-L1 in response to microorganisms and IFN- γ stimulation, thereby promoting the differentiation of CD4⁺CD8 $\alpha\alpha$ ⁺ IELs; The secretion of IL-22 and IFN- γ by IECs in PP modulates the expression of RegIII β and RegIII γ ; Immune-related active substances play an important role in anti-bacterial resistance to pathogen invasion.

The Role of Intestinal Mucosal Immune Barrier in SAP

The integrity of the intestinal mucosal barrier and intestinal immune function are closely related to the development of SAP.¹⁵⁹ Studies have shown that the intestinal mucosal immune barrier helps to prevent inflammation and pathogen invasion. As the integrity of the intestinal mucosal immune barrier is damaged, the release of endotoxin and D-lactic acid could aggravate the severity of SAP patients.^{160,161} And the complex process of inflammation and infection caused by intestinal mucosal barrier dysfunction in early SAP patients involves immunosuppression, the increase of regulatory T cells, and the release of related inflammatory cytokines.¹⁶² In ALI, the activity and function of innate immune cells (such as monocytes, macrophages and DC) mediated by T cell and B cell differentiation are regulated by SCFAs. Maintaining the balance of the immune system and alleviating the damage of the intestinal barrier and BT are important aspects of alleviating SAP-ALI.^{163,164} B10, a component of regulatory B cells, improves the severity of SAP.¹⁶⁵ In addition, bacterial translocation caused by intestinal flora disorder accelerates the development process of SAP.¹⁶⁶ The secretion of SIgA and lymphocytes in the gut during SAP can reduce the concentration of intestinal endotoxin and bacteria, thereby preventing bacterial translocation.¹⁶⁷ Studies have shown that oral administration of L-arginine can improve the intestinal mucosal immune functions by increasing the number of CD3⁺ and CD4⁺T lymphocytes and the concentration of SIgA in the lamina propria of the intestinal mucosa of SAP rats.¹⁶⁷ Notably, macrophages, as the major population of immune cells that migrate into the pancreas, appear to be particularly important in their function in controlling the immune responses.¹⁶⁸ Important roles of intestinal mucosal immunity include the recognition of harmful and infectious antigens, effective responses to destructive stimuli, the down-regulatory effects of immune responses to innocuous antigens, and the development of tolerance on which intestinal homeostasis depends. In summary, a deeper understanding of the intestinal mucosal immune barrier may provide new ideas for the clinical treatment of SAP.

Gut Microbiota and Intestinal Mucosal Immune Barrier

Relationships Between Gut Microbiota and Intestinal Mucosal Immunity

It is now generally accepted that gut microbiota co-evolves with the intestinal mucosal immune system and the former is thought to be a driving factor, which could train the immune system to defend against the pathogenic bacteria.¹⁶⁹ The commensal bacteria in gut and their derived metabolites could modulate the intestinal immune microenvironment and the development or maturation of a variety of immune cells, resulting in the enhancement of intestinal mucosal immunity.^{170,171} The disruption of the microbial community in the early stages of life has been found to alter the development of PP within the GALT and the formation of germinal centers, while fewer IELs, Tregs and SIgA were presented in germ-free mice.^{172,173} The stimulation of LPLs by *Lactobacillus* can induce the secretion of IL-22 and activate the STAT3 signaling pathway, thereby promoting the regeneration of ISCs and facilitating the renewal and repairment of IECs.¹⁷⁴ Additionally, the gut microbiota exerts an influence on the levels of conjugated linoleic acid within the mouse intestine, thereby augmenting the population of intraepithelial lymphocytes through a mechanism associated with the activation of transcription factors HNF4 γ and ThPOK.¹²⁵ SCFAs, the bioactive molecules by microbes, have been reported to assist in the maintenance of the intestinal barrier and modulation of innate immune cells, and these findings demonstrate their potential in attenuating the systemic inflammatory responses in SAP-ALI.¹⁰³ About ninety percent of SIgA in gut is produced by microbes, the diversity of which can be sensed by M cells as well as the microbe-associated molecular patterns (MAMPs).^{175,176} Studies have shown the gut microbiota may influence the mucus by regulating the expression of glycosyltransferases^{177,178} and the increased permeability in intestinal barrier may be strongly associated with the increased level of serum lipopolysaccharide.¹⁷⁹⁻¹⁸¹ Currently, the investigations in how the gut microbiota enhances bidirectional communications with the intestinal mucosal immune barrier in SAP-ALI remains a prominent area, and exosomes derived from gut bacteria are anticipated to emerge as a novel focal point.

Gut Microbiota and B-Lymphocytes

B-lymphocytes are secondary antigen-presenting cells, which could enhance the immune effect by the release of cytokines, and the stimulation of immunoglobulins. While, B cells have been proven to be activated by the secretion of intestinal epithelial cells by stimulation of bacteria. It is reported that IgA secreted by B-lymphocytes plays a key role

in the intestinal mucosal immune system, and Segmented Filamentous Bacteria (SFB) harbored in the flora could effectively stimulate the secretion and synthesis of IgA, thus facilitating the generation of immune responses.

Gut Microbiota and T-Lymphocytes

The differentiation of T cells can be regulated by gut microbiota via the stimulation of dendritic cells and macrophages, and the production of helper T lymphocytes. Regulatory T cells are important components of the immune system in the intestinal mucosa, which could promote the secretion of antimicrobial peptides and clear pathogens. Gut microbes perform a promoting effect on the differentiation and proliferation of regulatory T cells and their metabolites are capable of influencing the autoimmune regulatory responses.¹⁸² For example, *Clostridium perfringens* and *Bacteroides* could stimulate the proliferation and development of Treg. While, *Bifidobacterium* can promote the generation of Th17 in gut. Short-chain fatty acids, a type of metabolite derived from gut microbiota, act as the inhibitor of histone deacetylase and could induce the production of regulatory T cells by means of the G-protein-coupled receptor.¹⁸² Another group of metabolites, which are tryptophan metabolites, have been proven to perform the activities in inhibiting inflammatory responses via aryl hydrocarbon receptors in T cells or astrocytes.

Crosstalk Between Gut Microbiota and Intestinal Immunity

Gut microbiota maintains the integrity of the gut by regulating the permeability of the barrier and their normal functions, among which the Firmicutes and the Bacteroidetes are capable of absorbing the nutrients and promoting their motility while maintaining the structural integrity of the gut. Antimicrobial peptides secreted by pancreatic alveolar cells and Paneth cells are effective in maintaining intestinal integrity, as well as ensuring the intestinal barrier functions and maintaining intestinal immune integrity. While, the intestinal mucosal immune barrier is the bridge for bacterial translocation during SAP. In SAP, the pro-inflammatory and anti-inflammatory factors exhibit opposite effects with each other, such as increased expression of cytokines lost balances and the expression of several factors such as TNF- α , IL-1 β , IL-6, IL-17A, CXCL1 and IL-18 increased.^{183,184} A summary of the interactions between gut microbiota and intestinal mucosal immunity is shown in Figure 2.

Changes in Gut Microbiota During Sap

As an important part of the intestinal biological barrier, gut microbiota is involved in the development of SAP-ALI. This is also evidenced by the fact that the relatively sterile state of the ileum in the intestine significantly reduces the degree of pancreatic damage during AP.¹⁸⁵ Studies based on 16SrRNA gene sequencing have found that the abundance and diversity of intestinal flora are significantly varied in SAP. Specifically, the abundance of pathogenic bacteria such as *Escherichia*, *Shigella*, *Enterobacteriaceae*, *Enterococcus* and *Staphylococcus* is significantly increased, and the abundance and diversity of intestinal beneficial bacteria *Bifidobacterium* and *Akkermansia* are significantly reduced compared with the control group.^{50,186–188} At the phylum level, the increase in the relative abundance of *Bacteroidetes* and *Proteobacteria* and the decrease in the relative abundance of *Firmicutes* and *Actinobacteria* are important characteristics of gut microbiota in SAP.¹⁸⁹ At the genus level, abundance of *Phascolarctobacterium* significantly increased, and *Candidatus_Saccharimonas*, *Prevotellaceae*, *Lachnospiraceae*, and *Ruminiclostridium* were significantly reduced.⁸⁹ The data above suggested the potential role of gut microbiota in mediating SAP, as well as a prospective target for the treatment.

The Relationships Between Gut Microbiota and Sap

Several publications have reported the important regulatory role of gut microbiota in the occurrence and development of acute pancreatitis via the “gut-pancreas axis”.¹⁹⁰ The damage in the intestinal barrier and the increase in intestinal permeability caused by inflammation are considered important factors that affect the pathology of SAP.¹⁹¹ Bacterial translocation may aggravate SAP-ALI by the increase of oxidative stress levels and intestinal flora carrying pathogen-associated molecular patterns (PAMPs) can transfer from the lamina propria to the lungs once the intestinal barrier is damaged. This process also enhances the secretion of inflammatory molecules including IL-6 and TNF- α .^{192,193} In addition, there is a positive correlation between the abundance of *Enterobacter*, *Enterococcus* and the expression of inflammatory factors (IL-6 and TNF- α), suggesting the role of pathogenic bacteria in accelerating the inflammatory

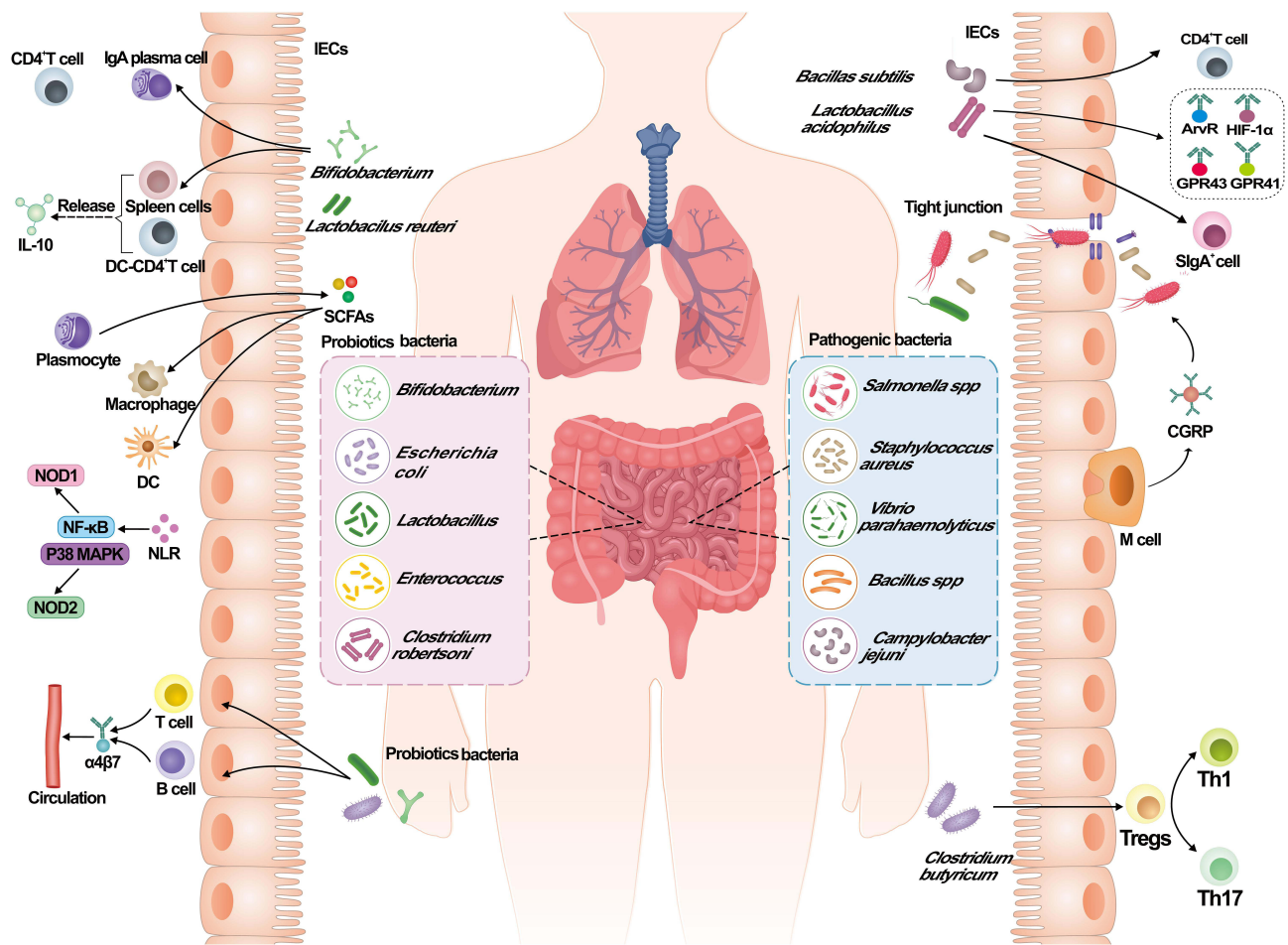


Figure 2 Interactions between gut microbiota and the intestinal mucosal immunity. Intestinal microorganisms in the body can be classified into two main categories: probiotic and pathogenic bacteria. Pathogenic bacteria include: *Salmonella spp*, *Staphylococcus aureus*, *Vibrio parahaemolyticus*, *Bacillus spp*, *Campylobacter jejuni*; The probiotic bacteria in the body could stimulate the expression of $\alpha 4\beta 7$ by T cells and B cells, then enter into the blood circulation; *Bifidobacterium* induce the expression of $CD4^+$ T cells, increase the number of IgA by plasma cells, and release IL-10 by the induction of spleen cells and DC- $CD4^+$ T cells; *Lactobacillus* could stimulate LPLs, thereby activating STAT3 signaling pathway and ISCs to enhance intestinal mucosal immunity; SCFAs produced by plasma cells could modulate the macrophages and dendritic cells to maintain the intestinal function; During SAP, the abundance of pathogenic bacteria increases and part of them could enter the body through the damaged tight junction; M cells play an important role in resistance to the pathogenic bacteria by targeting CGRP; *Lactobacillus acidophilus* combined with *Bacillus subtilis* can stimulate the production of $CD4^+$ T cells and $SlgA^+$ cells, resulting in the increase in GPR43, GPR41, AhR and HIF-1 α ; The presence of *Clostridium butyricum* could enhance the Treg response and suppress the Th1 and Th17 response.

responses under SAP-ALI.¹⁸⁸ The relative abundance of *Bacteroides* and *Prevotella*, which are important SCFAs-producing bacteria, decreased during SAP, resulting in the reduction of propionate, butyrate and valerate.¹⁸⁷ Butyrate can alleviate cerulein-induced AP and intestinal injury by inhibiting the interactions between HDAC and AP1, ATAT1 and the expression of NLRP3 inflammasome.¹⁹⁴ In addition, it has been shown that *Lactobacillus* can reduce the occurrence of pancreatic necrosis and pancreatic abscess, while *Akkermansia* is essential to form intestinal tight junctions and protect the intestinal barrier.^{195,196} Further research is required to investigate the impact of gut microbiota on SAP-ALI through the regulation of intestinal mucosal barrier function, specifically focusing on intestinal permeability and antimicrobial peptides.¹⁹⁷

Migration of Immune Cells via Gut-Lung Axis

The effector of gut microbiota on mucosal immunity is not limited to the gastrointestinal tract, but may also perform an impact on the distal mucosal sites, including the lungs. The pathways between the gut and lung tissues and the bidirectional regulations with each other through microbiological or immune systems are known as the “gut-lung axis”.¹⁹⁸ The stimulated immune cells within the intestinal mucosa could spread and migrate to other mucosal sites,

which is called the “common mucosal immune response”.¹⁹⁹ Previous studies have shown that immune cells from the gut, ILC2s, ILC3s, and Th17 cells, could be translocated from the gut to the lungs and participate the inflammation.²⁰⁰ Adhesion cascade reaction of immune cells is the key component of organismal immune cell migration.²⁰¹ The $\alpha 4\beta 7$ expressed on the surface of immune cells is a resting state in the non-inflammatory state and would not bind to the adhesion molecules on endothelial cells. While in the inflammatory state, L-selectin expressed by immune cells (mainly naive T cells) would bind to MAdCAM-1, which is highly expressed in the endothelial vein on GALT, allowing lymphocytes to slowly move along the vessel wall and expose the binding site for $\alpha 4\beta 7$, ultimately allowing immune cells to adhere to the endothelial cells and the cell cytoskeleton was altered.²⁰² Recent studies have found that BL-99 as prophylaxis could inhibit the growth of potential pathogens (*Burkholderia cepacia*, *Shigella* and *Clostridium perfringens*) and upregulate the expression of receptors associated with SCFAs, resulting in the decrease of inflammatory mediators and inflammatory immune cells (such as monocytes and macrophages) influx into the lungs.²⁰³ Studies have shown that SCFAs can improve inflammatory responses through the gut-lung axis during SAP, specifically, SCFAs regulate intestinal barrier function and reduce SAP-ALI through the AMPK/NF- κ B/NLRP3 mediated pathways.^{187,204} Succinic acid promotes alveolar macrophage polarization through its receptor SUCNR1 and downstream PI3K/AKT/HIF-1 α pathway, which also provides further evidence for the gut-lung axis in SAP.²⁰⁵ In addition, SCFAs can affect the expression of free fatty acid receptors FFAR2 and FFAR3 in lungs.²⁰⁶ The significance of the gut-lung axis in SAP-ALI cannot be disregarded, as evidenced by all these findings, and further explorations are still necessary to provide theoretical support for the clinical treatment.

Apart from this, immune cell migration has been reported to be accelerated by gut microbiota and their metabolites via the activation of signaling molecules (eg, IL-33, IL-25).^{207,208} The symbiotic intestinal immune system acts as an intermediate by regulating immunol signal pathways (such as NF- κ B, STING), and modulating the activity of T lymphocyte subsets. This enhances the communication between immune cells and epithelial cells in SAP-ALI. Details are shown in Figure 3. However, further molecular biology research is still required.²⁰⁹

Drugs and the Mechanisms

As mentioned previously, the intestinal mucosal immune barrier exhibits a protective effect in the development of SAP-ALI. Enhancing the functions of the intestinal mucosal immune barrier and inhibiting the translocation of bacteria or inflammatory factors via the gut-lung axis have been considered a promising direction in the treatment of SAP-ALI. Currently, available drugs that enhance the intestinal mucosal immune barrier include probiotics, glutamine, enteral nutrition, and traditional Chinese medicine.

Probiotics

Probiotics are a group of microbes that could help to maintain the balance of intestinal microecology and intestinal mucosal immunity, which could be colonized in the intestinal tract for a long time.²¹⁰ Current studies have demonstrated that a variety of intestinal probiotics, including *Bifidobacterium*, *Lactobacillus*, and *Clostridium butyricum*, exert protective effects in SAP-ALI, and mechanisms encompass multi-targeted modulation effects on the immune barrier of the intestinal mucosa.^{40,211–213} *Bifidobacteria*, mainly colonized in the intestinal mucus layer, could release specific metabolites and control the activity of GCs by increasing the expression of MUC2 and preventing the overgrowth of Enterobacteriaceae. At the same time, *Bifidobacteria* could improve the efficiency of PD-1, PD-L1 and influence the immune defense of the host.²¹⁴ Specific commensal *Bifidobacterium longum* can significantly upregulate the number of immune cells (CD4⁺ T cells, IgA plasma cells) and modulate the intestinal immune functions by Th1/Th2 and Th17/Treg.²¹⁵ In addition, AO44, a new strain of *Bifidobacterium longum* that enrich with extracellular vehicles has shown anti-inflammatory properties and it can induce the release of IL-10 by the splenocytes and DC-CD4⁺ T cell co-cultures.²¹⁶ *Lactobacillus rhamnosus* Probio-M9 strengthens the link between intestinal immune cells and commensal bacteria, which also stabilizes genetic variation within the gut microbiota.²¹⁷ *Lactobacillus Royale* can maintain the intestinal barrier integrity by activation of LPLs, STAT signaling pathway and regeneration of ISCs.¹⁷⁴ *Lactobacillus acidophilus* in combination with *Bacillus subtilis* modulates the intrinsic immunity in the intestine by upregulating the number of CD4⁺ T cells and SIgA⁺ cells, as well as the expression of GPR43 and GPR41, aryl hydrocarbon receptors, hypoxia-inducible factor 1 alpha and SIgA.²¹⁸ The abundance of pathogenic bacteria triggers *Clostridium butyricum* to enhance Treg responses through tolerogenic

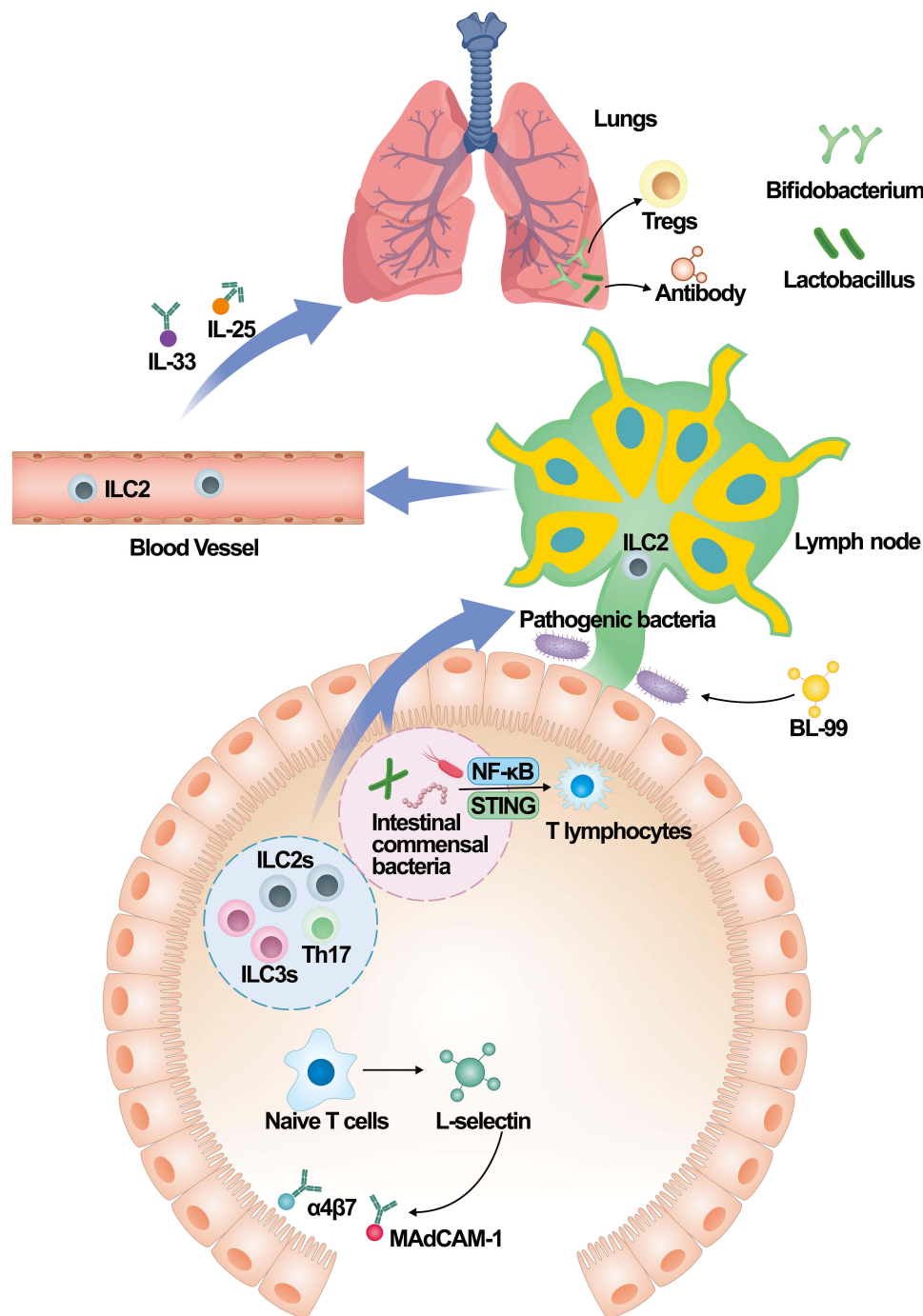


Figure 3 Immune cells along the gut-lung axis. Immune cells such as ILC2s, ILC3s and Th17 could transfer from the intestine to the lungs and participate in the inflammatory responses. The migration of immune cells is expedited by intestinal bacteria and their metabolites via IL-33 and IL-25; Intestinal bacteria could change the activity of T lymphocyte subsets through NF- κ B and STING signaling pathways; L-selectin expressed by naive T cells binds to MAdCAM-1, exposing binding sites for α 4 β 7 activation and ultimately altering the cytoskeleton; Pathogenic bacteria can be transferred to the lung through the gut-lung axis to trigger inflammatory responses, while probiotics could migrate to the lungs and reduce the inflammatory responses by the production of antibodies and enhancement of NK cells; *Bifidobacterium* enhances the inflammatory responses caused by the migration of pathogenic bacteria.

antigen presentation signals, while simultaneously suppressing Th1 and Th1.²¹⁹ The beneficial effects of probiotics on SAP have been demonstrated in previous studies, and it has been reported that probiotics can alleviate the pathological state of pancreatic tissue and reduce the infection rate in SAP rats by reducing the number of potentially harmful bacteria in the duodenum and

preventing the migration of intestinal bacteria to other organs such as the pancreas.²²⁰ While more studies are needed to determine whether it can be used as a potential target to attenuate the severity of SAP.^{221–223}

Glutamine

Glutamine (Gln) is a common amino acid in the human body and is thought to modulate systemic inflammatory responses while also playing a crucial role in various essential metabolic processes,^{224,225} and changes in levels have been reported to indicate the severity of diseases.^{226,227} Serving as a substrate for energy metabolism in IECs, Gln stimulates the differentiation and proliferation of ISCs, and maintains the morphological integrity of the mucosa in the small intestine.²²⁸ In addition, Gln is the energy source for numerous immune cells (such as macrophages, lymphocytes, fibroblasts, and monocytes) in the GALT and a precursor for cell proliferation, ensuring the activated status of immune cells and the resistance to the bacterial invasion, thus enhancing the non-specific immunol functions.^{226,229} Fasting under SAP might lead to the weakness of the mucus layer on the intestinal surface, increased intestinal permeability, and the translocation of bacteria and endotoxins, possibly attributing to entheogenic sepsis or multi-organ failure. While, this condition has been alleviated by the supplement of Gln.²²⁸ At present, it is still unknown whether glutamine use affects the abundance of intestinal flora during SAP and future studies can be carried out on whether it affects intestinal mucosal immune functions in SAP-ALI patients.²²⁶

Enteral Nutrition

Enteral nutrition (EN) is a safe route to provide nutritional support and stimulate the gastrointestinal motility of patients with SAP.²³⁰ The maintenance of cellular functions and integrity can be achieved through localized nutrient delivery, resulting in reduced incidence of stress mucosal disease and subsequent palliation of the condition.²³¹ Previous studies have demonstrated that EN can promote the production of transmembrane-binding proteins, protect the intestinal epithelium from tight junctions, and enhance the intestinal mucosal barrier.²³² EN can innate the immune responses by stimulating the intestine and facilitating the migration of $\alpha4\beta7$ and L-selectin towards PPs.²³³ In addition, enteral nutrition has been shown to effectively preserve the population of goblet cells (GCs) and sustain the expression levels of MUC2 and lysozyme.²³⁴ The administration of short-peptide-based enteral nutrition (SPEN) can ameliorate intestinal mucosal microcirculatory impairment by mitigating mucosal inflammation, preserving the integrity of the intestinal mucosal barrier and reversing the systemic immunosuppression.²³⁵ Arginine supplementation reduces the damage of intestinal mucosa, and stimulates the proliferation of immune cells within PP, and increases the secretion of intestinal IgA.²³⁶ However, it is crucial to consider the timing of administration, as there may not be a significant improvement in symptoms when administered within 24 hours compared to that between 24h and 48h,²³⁷ which needs further studies.

Traditional Chinese Medicine

The performance of traditional Chinese medicine in the management of SAP should not be underestimated, as it plays a pivotal role in attenuating inflammatory factors and improving the prognosis. Qing-Yi Decoction (QYD), composed of Rhubarb, Radix bupleuri, Radix Aucklandiae, Paeoniae Radix Alba, Natrii Sulfas, Rhizome Corydalis, Gardenia jasminoides and Scutellaria baicalensis Georgi. The formula is commonly employed in the treatment of SAP,^{238,239} previous studies have shown that QYD could protect the intestinal barrier by inhibiting the release of inflammatory factors, the production of endotoxin, and the expression of NF- κ B to block the activation of neutrophil cells.²⁴⁰ QYD could also improve gastrointestinal functions, reduce the infection rates, improve the prognosis and alleviate the lung injury in SAP patients,^{241,242} mechanisms of which may be related with the inhibition of secretory phospholipase A2 in the intestine and lungs.²⁴³ Recent studies have shown that the abundance of SCFAs produced bacteria increases after the treatment of QYD in SAP, and the produced SCFAs could regulate the AMPK/NF- κ B/NLRP3 pathway via gut-lung axis, resulting in the reduction of systemic inflammatory responses and restoration of barrier functions.¹⁸⁷ The protective effect of QYD against IECs injury in SAP may be related to the CaN/NFAT pathway.²⁴⁴ In addition, the TLR4/NF- κ B signaling pathway might also be inhibited by QYD, which in turn prevents the destruction of intestinal mucosa.²⁴⁵ In addition, Cheng Qi Tang appears to be an effective treatment that could reduce the mortality and improve the organ dysfunction symptom scores and abdominal discomfort in SAP patients.⁵ To sum up, the

investigations in the pathogenesis of SAP-ALI are still at the beginning stage, and in-depth studies are needed in the future.

Summary and Prospections

The growing emphasis on the gut-lung axis highlights the role of the intestinal mucosal immune barrier as a crucial “firewall” in SAP-ALI, especially the migration of immune cells and the translocation of bacteria and their PAMPs. The disruption of the intestinal mucosal immune barrier in SAP-ALI may lead to a reconfiguration of the intestinal microenvironment and an alteration in the composition of the gut microbiota, thereby impeding efforts to regain control over it. This review aims to provide a comprehensive overview of the involvement of various intestinal mucosal immune barrier compositions in the development of SAP-ALI through the gut-lung axis, intestinal flora, and immune-active substances. Future studies may focus on the movement of LPLs along the gut-lung axis, which particularly holds the potential to alter immune cell polarization in lung tissue as well as injury-related molecular patterns. In conclusion, to better understand the pathogenesis of SAP-ALI and improve the prognosis of patients, more studies are needed on the intestinal mucosal immune barrier in SAP-ALI.

Abbreviations

AhR, aryl hydrocarbon receptor; ALI, acute lung injury; AMPs, antimicrobial peptide; CGRP, calcitonin gene-related peptide; EEs, enteroendocrine cells; EN, enteral nutrition; GALT, gut-associated lymphoid tissue; GAPs, goblet cell-associated antigen passages; GCs, goblet cells; Gln, glutamine; GLP-1, glucagon-like peptide 1; HVEM, herpes virus entry mediator; IAECs, intestinal absorptive epithelial cells; IECs, intestinal epithelial cells; IELs, intestinal intraepithelial lymphocytes; ILCs, innate lymphoid cells; ISCs, intestinal stem cells; LECs, intestinal epithelial cells; Lgr5, leucine-rich repeat-containing G protein-coupled receptor 5; LPLs, lamina propria lymphocytes; M cells, microfold cells; MAMPs, microbe-associated molecular patterns; MLNs, mesenteric lymph nodes; MODS, multiple-organ dysfunction syndrome; MSCs, mesenchymal stromal cells; MZB1, B-1 cell-specific protein; NOX1, NADPH oxidase-1; PCs, Paneth cells; PD-L1, programmed death ligand-1; PP, Peyer patch; QYD, Qing-Yi Decoction; RGFs, RSPO3+GREM1+ fibroblasts; ROS, reactive oxygen species; SAP, severe acute pancreatitis; SAP-ALI, severe acute pancreatitis acute lung injury; SCF, stem cell factor; SIgA, secretory IgA; SIRS, systemic inflammatory response syndrome; SPEN, short-peptide-based enteral nutrition; TACs, transit amplifying cells.

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Disclosure

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