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Review

Intestinal barrier damage, systemic inflammatory response syndrome, and acute lung injury: A troublesome trio for acute pancreatitis

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ABSTRACT

Severe acute pancreatitis (SAP), a serious inflammatory disease of the pancreas, can easily lead to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndromes (MODS). Acute lung injury (ALI) is one of the most serious complications of SAP. However, the specific pathogenesis of SAP-associated ALI is not fully understood. Crosstalk and multi-mechanisms involving pancreatic necrosis, bacteremia, intestinal barrier failure, activation of inflammatory cascades and diffuse alveolar damage is the main reason for the unclear pathological mechanism of SAP-associated ALI. According to previous research on SAP-associated ALI in our laboratory and theories put forward by other scholars, we propose that the complex pattern of SAP-associated ALI is based on the "pancreas-intestine-inflammation/endotoxin-lung (P-I-I/E–L) pathway". In this review, we mainly concentrated on the specific details of the "P-I-I/E–L pathway" and the potential treatments or preventive measures for SAP-associated ALI.

1. Introduction

Acute pancreatitis (AP) is a sudden inflammation of the pancreas and can develop from local injury of the pancreas to SIRS, and/or organ failure. With the ever-changing contemporary social living standards and lifestyles, the incidence of AP keeps increasing yearly. A population-based cohort study showed that the global incidence of AP amounts to33.74 cases per 100000 person per year and the mortality rate as 1.16 per 100000 person per –year [1]. According to the latest Atlanta classification in 2012, though self-limited mild AP (MAP) patients are clinically frequent, only about 10 % of AP patients develop SAP, with a mortality rate of 10–15% [2].

ALI is the most frequent type of organ failure in the early and late phases of AP [3]. Sarr et al. showed that 60 % of AP patients die from acute respiratory distress syndrome (ARDS) within one week of onset [4], Therefore, an in-depth study of the pathogenesis of SAP-associated ALI is pivotal in ameliorating the prognosis of patients with SAP.

2. The starting point of SAP-associated ALI : pancreatic injury

The etiology of AP is complex and not easily recognized. The three most common causes are gallstones, heavy alcohol consumption, and hyperlipidemia [5]. Furthermore, some of the remote causes include cholangiopancreatography (ERCP), pancreatic tumors, and injured pancreatitis, which can also lead to local inflammation. Myriad of studies have been published on the pathogenesis of AP; however, most

Abbreviations: SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; NF-κB, nuclear factor κB; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; AP-1, activator protein-1; MAPK, mitogen-activated protein kinase; MPTP, mitochondrial permeability transition pore; DAMPs, damage-associated molecular patterns; HMGB1, high mobility group box 1 protein; PLA2, phospholipase A2; PAF, platelet-activating factor; AMs, alveolar macrophages; MPO, myeloperoxidase; IL-1β, interleukin-1β; IEC, intestinal epithelial cell; TNF-α, tumor necrosis factor-α; SlgA, secretory immanoglobulinA; PRRs, pattern recognition receptors; TLRs, toll-like receptors; NLRs, nod-like receptors; ML, mesenteric lymph; JAK, janus kinase; miRNA, micro-RNA; DAD, diffuse alveolar injury; PAMPs, pathogen-associated molecular patterns; AECs, alveolar epithelial cells; IP, intestinal permeability.

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theories focus on pancreatic acinar cell necrosis and the occurrence of early SIRS. Additionally, some of the hypotheses include activation of nuclear factor κB (NF-κB), zymogen activation, oxidative stress, high Ca^{2+} levels, and microcirculation dysfunction, which can indirectly or directly lead to intestinal barrier failure, SIRS and ALI.

2.1. Oxidative stress and Ca^{2+}

Extensive studies have suggested that Ca^{2+} overload and oxidative stress are early AP events. Both mechanisms strengthen the process of acinar cell necrosis. Both basic and clinical studies have confirmed the existence of oxidative stress during AP. Baser et al. recently reported a decrease in the total level of antioxidant in the serum of patients with mild AP (MAP), and these changes correlate with the inflammatory process and the severity of AP [6]. Dur et al. showed that lymphocyte DNA damage and oxidative stress are significantly aggravated in AP patients [7]. The direct effect of oxidative stress on the acinus represented by an increase in reactive oxygen species (ROS) leads to lipid, protein, and DNA damage. Indeed, ROS can also increase the activation of inflammatory signals, such as activator protein-1 (AP-1), signal transducer and activator of transcription 3 (STAT3), and mitogen-activated protein kinases (MAPKs) [8]. The cross-talk between ROS and other signal pathways magnify the inflammatory cascade in AP. Furthermore, recent studies have demonstrated that ROS may regulate intracellular Ca^{2+} status, thus affecting the process of pancreatic acinar cell necrosis. It is a known fact that intracellular Ca^{2+} signaling plays a crucial role in pancreatic pathophysiology. Toxic by-products of AP (such as bile acids or alcohol metabolites) promote the production of ROS and the release of Ca^{2+}, affecting pancreatic cells structure and function [9]. The sustained elevation of intracellular Ca^{2+} in AP occurs in two forms: through extracellular Ca^{2+} influx and the endoplasmic reticulum (ER) Ca^{2+} channels [10]. The process of store-operated Ca^{2+} entry (SOCE) is mediated by the stromal interaction molecule-1 (STIM1)-Orai complex. Interestingly, Orai1 is a redox-sensitive protein that may correlate with the generation of ROS. Also, ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (IP_3Rs) are predominant channels that release Ca^{2+} from ER into the cytoplasm. Some studies have shown that IP_3Rs and RyRs are related to oxidative stress [11]. Therefore, oxidative stress is a key regulator of Ca^{2+} levels in acinar cells. Altogether, these changes induce cell necrosis and inflammatory cascade.

2.2. Acinar cell organelles disorders

Recent studies have shown that disorders of acinar organelles are preeminent warning signs for the occurence of AP. The ER is highly developed in acinar cells and is the main site of protein synthesis, folding, and aggregation. Early ER stress (ERS) is a self-protective mechanism of acinar cells, but pathological or persistent ERS promotes AP. When ERS is continuously activated, acinar cells generally reduce these burdens by “unfolded protein response” (UPR) that increase activation of ER transmembrane proteins, including protein kinase RNA-like ER kinase (PERK), inositol requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and expression of the glucose-regulated protein (GRP78) [12]. Furthermore, persistent ERS can induce cell apoptosis by modulating caspase-related pathways. Liu and his colleagues found that the major markers of ERS (C/EBP homologous protein, GRP78, and p-IRE1) are activated early in the arginine model of AP [13]. Tam et al. showed that the PERK/IRE1 mechanisms could regulate NF-κB activation which mediates the expression of inflammatory factors [14]. Zhou et al. observed that p53, which may be triggered by ER stress in pancreatic tissues, promotes acinar cell apoptosis and the progression of AP [15]. Mitochondria are responsible for a range of cellular functions; their foremost function being the generation of ATP. Early responses of AP involve ROS and Ca^{2+} overload which can cause the opening of mitochondrial permeability transition pore (MPTP) channels, resulting in mitochondrial structural damage and ATP depletion [16]. Lysosomes are dynamic organelles where catabolism of macromolecules occurs. Autophagy takes place in this organelle, as well as the breakdown of damaged organelles and macromolecules trafficked via endocytosis, Autophagy is evolutionarily conserved and maintains pancreatic acinar cell function. Antonucci et al. stated that vacuolation caused by impaired autophagy has become a signature response of AP [17]. Biczo et al. showed that strategies for restoring autophagic function largely work by preventing trypsinogen activation and necrosis, which eventually relieves pancreatic injury in experimental AP [18]. After acinar cell necrosis, the greatest contribution to the inflammatory response is the release of massive damage-associated molecular patterns (DAMPs) such as high mobility group box 1 protein (HMGB1) which maintains and amplifies the inflammatory cascade by binding to a variety of downstream receptors (we will elaborate on this paragraph in Chapter 3). In short, multiple parallel mechanisms, including impaired lysosomal function, mitochondrial failure, and ERS are now recognized to be momentous in driving SIRS and distant organ injury in AP.

2.3. Zymogen activation

The premature activation of zymogen is an important hallmark event in AP and relates to intestinal barrier failure and ALI. Although there are various causes of AP, however, they all share a common pathological process,that is the destruction of acinar cells and abnormal activation of trypsin induce “self-digestion” of the pancreas, which eventually results to AP. Recent studies have shown that trypsin may be the culprit of multiple organs dysfunction in SAP. On the one hand, activated trypsin causes pancreatic bleeding and necrosis, hindering perfusion of blood from the circulation into the target organs and leading to organ damage and dysfunction [19]; on the other hand, trypsin indirectly causes distal organ damage by promoting inflammatory cascade reaction [20]. Zhou and his colleagues confirmed that excessive activation and release of phospholipase A2 (PLA_2) during AP can destroy alveolar surfactant, promote the accumulation of platelet-activating factor (PAF) and eicosanoic acid in the lung, leading to the disturbance of alveolar function and continuous occurrence of pulmonary inflammatory response [21]. Tsukahara et al. found that PLA_2 may induce significant amounts of NO production and inducible NO synthase (iNOS) mRNA expression in alveolar macrophages (AMs), aggravating the development of ALI [22]. Maeda et al. suggested that trypsin and its specific receptor, protease-activated receptor-2 (PAR2), play a crucial role in cytokine production and the activation of inflammatory cells during AP [23]. Subsequent studies confirmed that trypsin and PAR2 can promote the activity of myeloperoxidase (MPO) in the lung tissue during AP, and their inhibitors significantly reverse this phenomenon [24]. Some scholars believe that zymogen activation is a necessary step in SIRS during AP. On getting into the blood circulation, trypsin stimulates macrophages to release a large amount of pro-inflammatory factors that trigger the inflammatory cascade reaction, and lead to SIRS [20]. Furthermore, inflammatory mediators such as thromboxane A_2 (TXA_2), PAF, and endothelin-1 (ET-1) regulated by PLA_2 and interleukin-1β (IL-1β) can cause vasospasm, aggregations of leucocytes, and platelets, thrombosis and injury of vascular endothelial cells, leading to loss of the intestinal barrier [25]. Therefore, trypsin may be a significant initiator/mediator for the local and systemic effects of AP.

2.4. Pancreatic microcirculatory disturbance

The disturbance of the pancreatic microcirculation initiates and aggravates AP. Furthermore, the effect extends beyond the pancreas and leads to intestinal barrier failure and lung injury [26]. Early events such as Ca^{2+} overload, inflammatory mediators, and zymogen activation injure pancreatic intralobular arterial sphincter and the vascular endothelial cells, causes pancreatic vasoconstriction, shunt, and insufficient perfusion. The effects of pancreatic microcirculatory disturbance in SAP

are complex and include severe pancreatic edema, edema in peripancreatic and retroperitoneal tissues, massive extravasation of tissue fluid, the third space effect/sequestration, and excitation of the renin-angiotensin system, consequently leading to ischemia and hypoxia in other organs [27]. Intestinal mucosa tissue is most susceptible to impaired perfusion and oxygen delivery. Following intestinal ischemia caused by microcirculation disorder, xanthine oxidase and hypoxanthine accumulate in the intestinal tissue, and ATP is depleted due to insufficient oxidative phosphorylation. In subsequent reperfusion, the transformation of hypoxanthine to xanthine releases superoxide ions, which leads to the production of more free oxygen radicals causing lipid peroxidation-cell membrane damage [28]. In short, these pathological changes accelerate the loss of intestinal barrier. Furthermore, Liu et al. found that SAP changes the hemodynamics of rats, leading to severe microcirculatory disorders in the pancreas and other organs (especially lung) [29]. This finding suggests that the numerous pathological changes seen in the microcirculation of the lungs, such as increase in vascular endothelial cell space and permeability, aggregation of marginal concentration of leukocytes, and profuse expression of intercellular cell adhesion molecule-1 (ICAM-1), play a crucial role in the occurrence and aggravation of ALI.

In conclusion, acinar cell necrosis and inflammation are induced by oxidative stress, Ca^{2+} overload, organelles disorders, early activation of trypsin, activation of NF-κ B, AP-1, and MAPK signaling pathways, and accumulation of inflammatory cells [30,31]. Additionally, DAMPs released by necrotic acinar cells, leakage of activated trypsin, and hemodynamic changes induced by microcirculation disturbance all promote the occurrence and development of the "P-I-I/E–L pathway" (Fig. 1).

3. The gas station of SAP-associated ALI : intestinal barrier failure

3.1. Intestinal mechanical barrier

The intestinal mechanical barrier is composed of the intestinal epithelial cell (IEC) and intercellular junctions. The IEC is made of Paneth cells, enteroendocrine cells, mucus-producing goblet cells, and absorptive enterocytes and separates the intestinal cavity from the lamina propria. The tight junction (TJ) is composed of occlusive protein (Occludin), synaptic connexin (Claudin), junction adhesion molecule (JAMS), and occlusive protein (ZO-1). The TJ which is located at the top of the intercellular junction, mainly occludes the intercellular space, and is the primary determinant of paracellular permeability [32]. High-speed turnover of IECs every 4–5 days ensures normal digestion and barrier function, and is based on non-inflammatory apoptosis [33]. Excessive IEC apoptosis and uncontrolled inflammatory response are the characteristics of intestinal barrier failure in SAP. It was pointed out earlier that local pancreatic injury leads to microcirculatory disturbance and waterfall-style release of inflammatory mediators. Tian et al. confirmed that inflammatory factors such as tumor necrosis factor-α (TNF-α), and intestinal mucosal ischemia-reperfusion injury cause severe oxidative stress and activation of caspase-3 pathway, leading to severe apoptosis of the intestinal mucosa cells [34]. Furthermore, large amount of HMGB1 released by necrotic acinar cells can affect the physical barrier function of the intestinal mucosa. Subsequent studies have shown that HMGB1 inhibition reduces intestinal permeability (IP) by preserving the expression of TJ (such as claudin-2 and occludin), thus reducing the severity of SAP [35]. Xian and his colleagues found that the expression levels of claudin-4 in lung tissue samples are significantly decreased [36]. Interestingly, other studies proposed that decreased expression of Claudin-4 protein may be the possible mechanism for

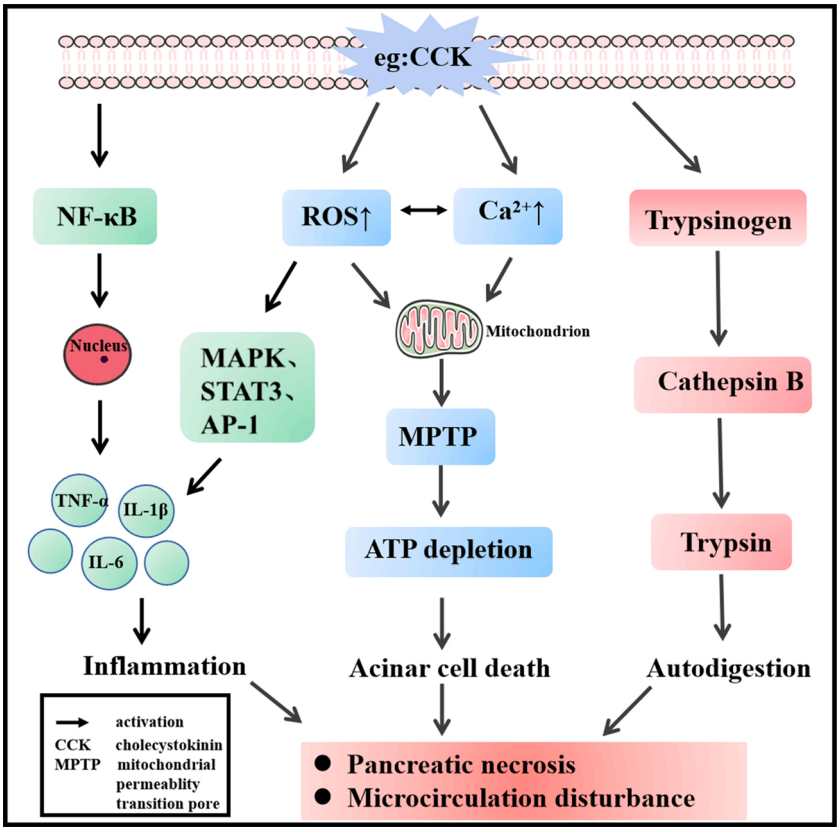

Fig. 1. The early events of pancreatic injury. Acinar cell necrosis and microcirculation disturbance being induced through oxidative stress, Ca2+ overload, organelles disorders, early activation of trypsin, activation of NF-κ B, AP-1, and MAPK signals, and accumulation of inflammatory cells.

increased IP [37]. Aquaporins (AQPs) are a class of membrane water channels, and play a key role in maintaining water homeostasis of lung and intestine. Kang et al. showed that AQP1, AQP5 of the lung, and AQP1, AQP5 of the intestine in the model group were significantly decreased [38]. This finding suggested a probable connection between the intestines and lungs during SAP.

3.2. Intestinal chemical barrier

Intestinal chemical barrier comprises of mucins (MUC), antimicrobial peptides (AMPs), and other digestive enzymes. AMPs are a kind of polypeptides secreted by Paneth cells, which have the functions of sterilization, anti-inflammation, and promotion of tissue repair. Chen et al. showed that the decrease of AMPs may participate in the occurrence of intestinal barrier failure during ANP [39]. Also, AMPs play a crucial role in bacterial translocation in AP. The decrease of intestinal AMPs (especially β-defensins) in AP may increase the rate of intestinal bacterial translocation and increase the possibility of retrograde infection [40]. MUC2, a main component of the intestinal chemical barrier covers the IEC and forms the intestinal mucus layer. This is the first line of the intestinal mucosal barrier [41]. The intestinal mucus layer contains inner and outer layers, which mainly accelerate the absorption of nutrients, provide adhesion sites for symbiotic bacteria, and limit the binding of pathogens to IEC [42]. Many studies have shown that the mucus layer is not only a barrier between intestinal contents and IEC but also critical in maintaining and restoring intestinal barrier function. Fishman and his colleagues showed that the indirect effect of AP (ROS-and RNI-mediated mucus layer loss) is associated with intestinal barrier failure [43]. Interestingly, this process can take place without the involvement of pancreatic proteases. Furthermore, Fishman et al. indicated that the mucus layer and the pancreatic proteases contribute to intestine and intestine-induced lung injury in rats with trauma-hemorrhagic shock [44].

3.3. Intestinal biological barrier

The intestinal biological barrier is a bacterial membrane barrier formed by the close adhesion of symbiotic bacteria (such as Bifidobacterium and Lactobacillus) to the surface of intestinal epithelial mucosa, which can resist pathogenic bacteria [32]. Symbiotic bacteria play a crucial role in regulating intestinal barrier function and the host health. Their functions include: 1. they promote the formation of the intestinal mucous layer and secretion of secretory immunoglobulin A (sIgA), which maintain intestinal immune response ; 2. Adhere to IEC through competitive mucosal sites forming a bacterial membrane barrier against foreign pathogens [45]; 3. Increase the proliferation of TJs, thus ensuring IP [46]; 4. Promote the expression of anti-inflammatory genes, reducing inflammatory reaction to IEC [47]. Furthermore, microorganisms benefit the host by synthesizing short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate. Kelly et al. found that bacteria-derived butyric can stabilize the expression of hypoxia-inducible factor (HIF) and its target genes, thus strengthening the IEC barrier [48]. Claudin-2 is a negative regulatory molecule of the intestinal barrier, which can promote intestinal inflammation and leakage. Zheng et al. showed that bacteria-derived butyric can inhibit the expression of Claudin-2 through the IL-10RA-dependent mechanism, thus protecting the intestinal barrier [49].

Myriad of studies showed that the intestinal microbiota is altered significantly during AP. A retrospective clinical study (108 participants) revealed that intestinal microbiota are altered in patients with SAP, here Enterococcus increases and Bifidobacterium decreases, and they correlate with inflammation, multiple organ failure(MOF), and infectious complications in SAP [50]. Zhu et al. found that abundance of beneficial bacteria such as Blautia, decreases with the severity of AP. On the contrary, the result of Escherichia coli-Shigella is the opposite and is related to IEC damage. The overall results showed that dysbiosis of intestinal microflora is correlated with AP severity [51]. Intestinal barrier function is impaired due to the disturbance of intestinal flora during AP. On the one hand, it is characterized by pathogen increase which aggravates TNF-α-mediated inflammation and decrease the expression of TJs, thus directly leading to IEC damage [52]. On the other hand, the decrease of beneficial bacteria reduces the competitive colonization of IEC and greatly increase the chance of pathogens in invading the intestinal mucosa [50]. The significant changes in intestinal microorganisms during AP can destroy the mucus layer and the bacterial membrane barrier of the intestinal mucosa, significantly aggravating AP and intestinal barrier failure.

In reality, the influence of bacterial translocation in SAP is very extensive. On the one hand, bacteria and endotoxins can cause a series of chain reactions after passing through IEC into the systemic circulation, including binding to pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and nod-like receptors (NLRs), activating NF-κB, MAPK and interferon regulatory factor (IRF) pathways, and stimulating the production of various cytokines such as TNF-α, IL-6, and IL-12. Finally, they magnify the inflammatory cascade and promote the occurrence of SIRS and MODS [53]. On the other hand, a clinical study (154 patients with pancreatic parenchyma necrosis) showed that bacteremia is related with an increased risk of pancreatic infection and necrosis(65 versus 37.9 percent; $P = 0.002$) [54]. Multiple studies have suggested that MODS and pancreatic necrosis infection increase the mortality of SAP [55,56]. Therefore, bacterial translocation caused by intestinal barrier failure is an important factor in pancreatic infection and MODS of SAP.

3.4. Intestinal immune barrier

The intestinal immune barrier consists of gut-associated lymphoid tissue (GALT) and scattered immune cells. The GALT is an inductive site that consists of Pyle collecting lymph nodes (PP), isolated lymphoid follicles (ILF), and mesenteric lymph nodes (MLN). Scattered immune cells are the effector sites and consists of the intraepithelial lymphocytes (IEL) and the lamina propria lymphocytes (LPLS) [57]. The intestinal mucosa is constantly exposed to exogenous antigens from food and intestinal microorganisms. As such, sIgA is secreted by intestinal immune tissue, ensures the balance of intestinal immune homeostasis [58]. sIgA is the most abundant antibody in the intestinal mucosal immune system and maintains the balance between symbiotic microorganisms and pathogens on the mucosal surface [59]. Furthermore, intestinal leakage and bacterial translocation are more likely to occur due to the absence of sIgA [60]. In reality, intestinal immune barrier can be significantly inhibited during SAP due to intestinal mucosal ischemia, hypoxia and excessive apoptosis. These effects are brought about by flora imbalance, oxidative stress, and outbreak of inflammatory factors. Qiao et al. found that the decrease in the number of lymphocytes and sIgA in the intestine during AP may be related to bacterial translocation [61]. Furthermore, current studies have shown that the relationship between intestinal microorganisms and sIgA is bi-directional. While sIgA stabilizes intestinal microenvironment, microflora also regulates the production and distribution of sIgA [62].

3.5. Mesenteric lymph (ML)

The intestinal lymphatic vessels provide a direct anatomical connection between the gut and the lung. ML avoids the portal circulation and directly transports immune cells, intestinal fluid, and chylus to the systemic circulation. Similarly, toxic components in the intestinal cavity, including toxins, trypsin, activated cytokines and immune cells seep directly into the pulmonary circulation through the ML [63]. The above process is called the “gut-ML-lung axis” and plays an important role in SAP-associated ALI. Aydin et al. demonstrated a 100 percent bacterial translocation into the mesentery lymph node [64]. Mole et al. showed that mesenteric lymph-borne kynurenines could promote MOF

induced by AP [65]. MiR-216a is an endogenous small RNA fragment that regulates gene expression. Plasma miR-216a levels are considered to be a biomarker for the early diagnosis of SAP [66,67]. Blenkiron et al. found that the levels of miR-216a are significantly increased in both ML and plasma of patients with AP, and have a certain correlation with the severity of AP [68]. Therefore, the "gut-ML-lung axis" plays a crucial role in the pathogenesis of SAP.

Furthermore, there are many studies on the relationship between intestines and lungs during SAP. Mittal et al. found that pancreas, lung, and jejunum show obvious early mitochondrial dysfunction in the AP model, however, mitochondria in the cells of the heart, the liver, the kidney, and the duodenum are not affected. This selective pathological mechanism may indicate the potential relationship between the intestine and lung during AP [69]. Regenerative gene I (RegI) is an effective biomarker of the severity of SAP-associated ALI. Hu et al. found that RegI is significantly upregulated in the intestinal tissue of AP animal models and have a positive correlation with the severity of intestinal injury [70]. Guo et al. found that electro-acupuncture (EA) treatment could ameliorate SAP-associated ALI by inhibiting vasoactive intestinal peptide (VIP) and MPO, while promoting the expression of CCK, intestinal propulsion rate (IPR), and regulating pro-inflammatory and anti-inflammatory mediators [71].

In conclusion, the intestine is easily damaged during AP [72], and IP has a certain prognostic value for SAP [73]. This condition seems to be more common in elderly patients with severe acute pancreatitis [74]. However, intestines are not the only "victims" of AP. The effects of intestinal barrier failure, such as intestinal immune deficiency, increased IP and intestinal microflora disturbance, maintain and amplify SIRS. Additionally, inflammation in the intestine connects to the pancreas, and then lungs through the systemic circulation and ML pathway, eventually leading to and aggravating ALI [75] (Fig. 2).

4. The hub of SAP-associated ALI : SIRS

The early events mentioned in section 1 (such as the activation of NF-κB [76] and trypsin activation) lead to local inflammation, in which necrotic tissues and cells release many inflammatory mediators (like IL-1β, TNF-α, and HMGB1), accompanied by the activation of inflammatory cells and the release of chemokine, adhesion molecules, oxygen-free radicals, PAF, and endothelin, escalating local inflammation to SIRS [77–79]. In the second section, we mentioned that SAP often leads to intestinal barrier failure, and toxic substances such as endotoxin and PLA_2 maintain and amplify the inflammatory cascade reaction through the systemic circulation and the mesenteric lymph pathway, resulting in more severe SIRS or sepsis [53]. In addition, Bonjoch et al. found that exosomes (A new intercellular communication system that transmits proteins, lipids, and miRNA to distant organs) participate in SAP-associated ALI by promoting macrophage polarization, which may be relevant mediators in the systemic effects of pancreatitis [80].

4.1. Cytokines

4.1.1. Tumor necrosis factor-α (TNF-α)

TNF-α is a potent pro-inflammatory mediator secreted by monocytes/ macrophages, which often cooperates with IL-1 β and IL-6 to induce inflammatory cascade in SAP-associated ALI. Zhu et al. demonstrated two kinds of TNF-α levels (highand low) in patients with SAP, and that high-level TNF-α may reduce lung function [81]. Perides et al. showed that therapies targeting TNF-α expression are effective therapeutic strategy for SAP [82]. In fact, TNF-α promotes the process of SAP-associated ALI in many ways. Firstly, after stimulation, acinar cells promote the release of TNF-α [83]. Secondly, the released TNF-α binds to pro-inflammatory receptors (like TNFR1) to initiate intracellular

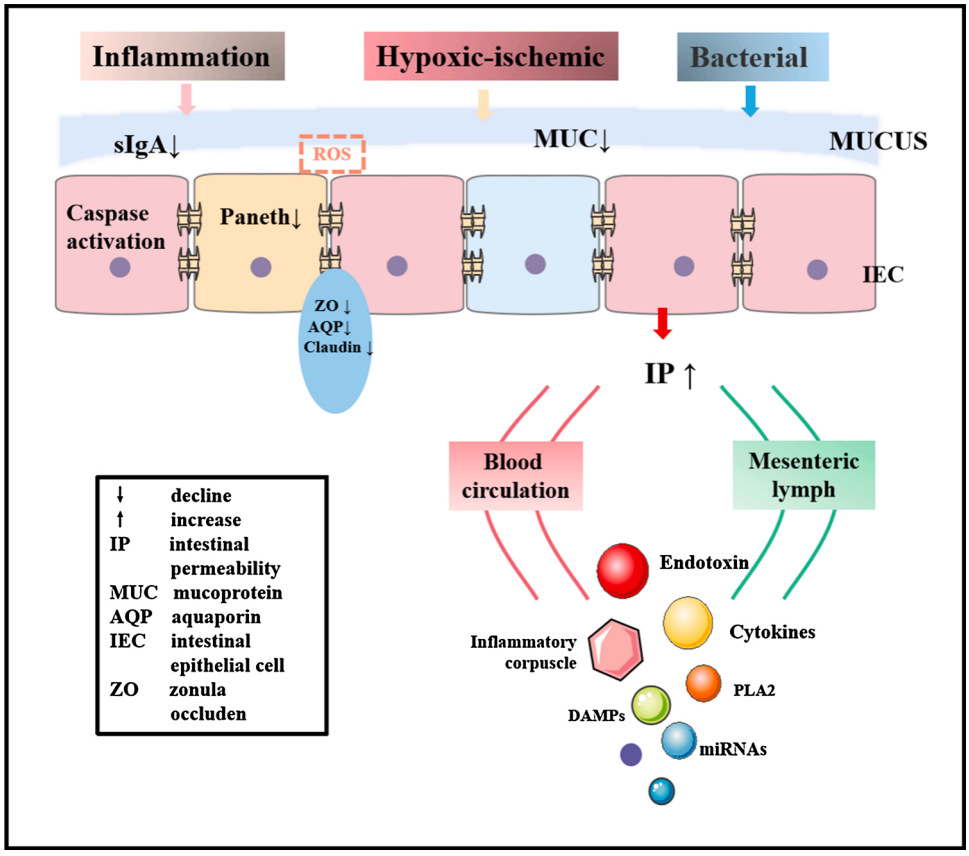

Fig. 2. The events of intestinal injury during severe acute pancreatitis. The effects of intestinal barrier failure in SAP, such as intestinal immune deficiency, increased IP, intestinal microflora disturbance, and excessive release of inflammatory mediators (like endotoxin, cytokines, DAMPs, and mRNAs).

pro-inflammatory signals such as p38MAPK, AP-1, and NF- κB [84,85]. Finally, these inflammatory signals (especially NF- κB [86]) further release inflammatory mediators such as IL-1 β, IL-6, and TNF- α. This malignant loop maintains and amplifies the inflammatory cascade, which plays a crucial role in the early stage of AP. In the lung, on the one hand, TNF-α destroys the endothelial cell barrier by regulating the expression of ICAM-1, adhesion molecule-1 (PECAM-1), and vascular cell adhesion molecule-1 (VCAM-1) and promote leukocyte trans-endothelial migration and ROS generation [87]; On the other hand, alveolar sphingomyelinase secreted in response to TNF-α inhibits the role of pulmonary surfactant [88]. Recent studies have suggested that TNF-α can stimulate ATII cells to downregulate genes related to surfactant and alveolar fluid clearance [89].

4.1.2. IL-1

IL-1 is a pro-inflammatory cytokine derived from macrophages, and composes of IL-1α and IL-β. TNF- α and IL-1 β promote the secretion of each other and jointly induce the inflammation cascade reaction. Blocking IL-1β significantly reduces pancreatitis and organ failure [90]. Inflammasomes are a class of macromolecular polyprotein complex, which mediate the activation of inflammatory mediators and the occurrence of inflammatory response. Among these inflammasomes, NLRP3 has received more attention in SAP. NLRP3 consists of NLRP3 scaffold, adaptor apoptosis speck-like protein (ASC), and the effector procaspase-1. Once stimulated, NLRP3 promotes the conversion of procaspase-1 to active caspase-1 by interacting with ASC and then regulates the cleavage of IL-1β and IL-18 (representative mediators of the inflammatory response in SAP [91]) into their active forms, promoting inflammation [92]. Hoque et al. showed that the components of ASC, caspase-1, and NLRP3 are necessary conditions for inflammation in AP; inhibition of TLR9, and P2 × 7 (important receptors upstream of NLRP3) significantly reduce pancreatic necrosis and lung inflammation [93]. Xu et al. demonstrated that NLRP3 participate in intestinal injury of SAP through caspase-1 pathway [94]. Wu et al. observed that the pyroptosis of alveolar macrophages induced by plasma exocrine-mediated NLRP3 pathway is an important mechanism of SAP-associated ALI [95]. IL-33, a member of the IL-1 superfamily and discovered by Schmitz in 2005 [96], has been shown to increase ERK activation, IL-6, CXCL2/MIP-2α, and CCL2/MCP-1 production in the lungs during AP [97]. IL-33 induces the expression of matrix metalloproteinase 2 (MMP2) and MMP9 in a stat3-dependent manner, aggravating pulmonary inflammation in alveolar macrophages of LPS-induced ALI [98]. Lin et al. found that neutralizing IL-33 significantly reduces pulmonary inflammation and injury in ARDS model [99]. Therefore, IL-33 plays an important role in SAP-associated ALI and most likely a new therapeutic target.

4.1.3. IL-6

IL-6 serum level is a reliable indicator of the severity of AP and can predict organ failure and SAP [100]. A prospective cohort study showed that serum IL-6 > 160 ng/ml significantly improve the predictive value of SIRS in SAP [101]. Janus kinase (JAK)/STAT pathway is the main effect pathway of inflammatory response. Firstly, the pro-inflammatory factor binds to the corresponding receptor and activates JAK. Secondly, JAK selectively phosphorylates STAT. Thirdly, the activated STATs are transferred into the nucleus to regulate the transcription of cytokines genes [102]. Zhang et al. found that the complex formed by IL-6 and soluble IL-6 receptor (sIL-6R) promotes the process of SAP-related ALI by activating STAT3 pathway through trans-signaling [103]. Earlier studies suggested that the JAK2/STAT3 pathway participates in the inflammatory response of AP by promoting the production of cytokines such as IL-1β [104]. Zhao et al. demonstrated that activation of STAT3 in the LPS-induced ALI model accelerates the severity of inflammation. LLL12 (STAT3 inhibitor) inhibits STAT3 phosphorylation and the expression of inflammatory mediators such as IL-1β, TNF-α, iNOS, and CCL2. These results suggest that STAT3 inhibition pathway is feasible for the treatment of SAP-associated ALI [105].

4.2. HMGB1

HMGB1 is a pro-inflammatory mediator that can be released by necrotic acinar cells and trigger the earliest inflammatory response of AP [106]. A great deal of evidence suggests that the level of HMGBl in patients can be used as an important indicator to determine the process of SAP [107,108]. Wang et al. revealed that trypsinogen activation peptide (TAP) can also induce HMGB1 release from pancreatic acinar cells [109]. The receptor of advanced glycation end products (RAGE) and TLRs play an important role in HMGB1-mediated inflammatory signal transduction [110,111]. Toll-like receptor (TLR)-4 is the crucial receptor for the recognition of pathogen-associated molecular patterns (PAMPs). Matsuda et al. first expounded the role of TLR-4 in SAP associated ALI [112]. The overstated pulmonary expression of TLR-4 induced by MIF plays a crucial role in the occurrence and development of lung injury. Awla et al. found that the absence of TLR4 significantly reduces the activity of MPO in lung tissue and the levels of serum CXCL2 in the SAP model. This study suggested that targeting the TLR4 pathway may provide a valuable therapeutic option against lung injury in SAP [113]. Sharif et al. verified this, their research showed that the absence of TLR4 significantly reduces SAP-associated ALI. Moreover, they also proposed that LPS is not a necessary factor needed by TLR4 to play its pro-inflammatory role [114]. Li et al. showed that HMGB1 can also activate TLR4, and then activate the NF-κB signal through the MyD88-dependent pathway and TRIF-dependent pathway to release inflammatory mediators and promote the occurrence of SAP [115]. HMGB1 can also induce the activation of the JAK2/STAT3 signal pathway and further magnify the inflammatory cascade. Chen et al. found that the expression of HMGB1 is positively related to intestinal barrier failure and inhibition of HMGB1 can significantly improve intestinal injury [116]. Blocking of HMGB1 can also promote the expression of TJs (claudin-2, occludin) and improve bacterial translocation [35]. Luan et al. demonstrated that down-regulating HMGB1 could inhibit the activity of NF-κB, the expression of MMP-9 and ICAM-1 in the lung tissue, and thus reduce the severity of SAP-associated ALI [117]. It should be noted that hepatocyte is an important source of circulating HMGB1 in SAP [118]. Therefore, the role of liver in SAP needs to be studied.

4.3. Non-coding RNA

4.3.1. Micro-RNA (miRNA)

MiRNA is a single-stranded non-coding RNA molecule, which is an important mediator for many inflammatory diseases [119]. MiRNA is involved in the regulation of inflammatory response and organ dysfunction in SAP. Zhang et al. found that the serum miR-216a level is positively associated with the pancreatic histopathological severity scores, and the plasma miR-216a level is helpful to identify SAP patients [66]. Zhao et al. showed that miR-375 promotes inflammation and apoptosis of acinar cells and regulates the development of SAP by targeting ATG7 [120]. Wang et al. found that upregulated miR-21-3p can promote the expression of serum enzymes and inflammatory factors in acute hemorrhagic necrotizing pancreatitis (AHNP) models, and aggravate pancreatitis and lung injury in AP by activating the transient receptor potential (TRP) signaling pathway [121]. Macrophages (peritoneal macrophage [80], alveolar macrophages [95], pulmonary intravascular macrophages [122]) play an important role in immune regulation of SAP-associated ALI. Zhao et al. showed that the differentially expressed miRNAs carried by exosomes are secreted by activated pancreatic acinar cells, and these miRNAs promote inflammation by enhancing the activation of NF-κB and MAPK in macrophages [123]. Wang et al. found that increased levels of miR-155 are substantially correlated with SAP, and inhibition of miR-155 may regulate the Th17/Treg ratio and inhibit the release of inflammatory factors by targeting SOCS1 [124]. Silent information regulator 1 (SIRT1) is an NAD^+-dependent deacetylase, which plays a crucial role in apoptosis,

oxidation, and inhibition of inflammation. It has been reported that the serum SIRT1 levels can be employed as an early predictor of persistent organ failure (POF) in patients with SAP [125]. Shi et al. found that SRT1720 (SIRT1 activator) protects SAP in experimental models, by inhibiting the NF- κB signal pathway [126]. Numerous studies have confirmed SIRT1 as a target gene of miR-155. Tuerdi et al. found that downregulation of miR-155 reduces septic-induced ALI by targeting SIRT1 in both vivo and in vitro studies [127]. Furthermore, Pasca et al. suggested that miR-155 is involved in regulating M1 polarization [128]. Interestingly, miRNAs have a beneficial side in SAP-related ALI. Upregulation of miR-542-5p can combine with PAK1 to inhibit the inflammatory response caused by the MAPK signal pathway, thus improving ALI in SAP mice [129].

4.3.2. *Long non-coding RNA (lncRNA)*

LncRNAs are the largest non-coding RNA population and regulate transcriptional and post-transcriptional gene expression through various mechanisms [130]. In recent years, the role of lncRNAs in SAP have been gradually noticed. A population-based study (180 acute pancreatitis) shows that long non-coding RNA intersectin 1–2 (lnc-ITSN1–2) might be a better biomarker for the distinction of SAP [131]. Wang et al. found that the levels of lncRNA B3GALT5-AS1 in AP patients are significantly lower than those in controls, and also in vitro studies show that overexpression of B3GALT5-AS1 may reduce cerulenin-induced AR42 J cell injury by regulating the miR-203/NFIL3 axis and inhibiting NF-κB signaling [132]. Gu et al. confirmed that the overexpression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) or yes-associated protein 1 (YAP1) significantly increases the secretion of IL-6 and TNF-α, but miR-194 can counteract this effect. This study showed that the loop mechanism among MATAL1, miR-194, and YAP1 dynamically regulate the progress of AP [133]. Therefore, the lncRNA-miRNA- protein pathway may be a key target for the diagnosis and treatment of SAP, and further exploration and research will be of great value.

4.4. *Others*

In addition to the above inflammatory mediators, other DAMPs released by necrotic acinar cells also play an important role in amplifying SAP-associated ALI [134]. Dixit et al. found that released ATP from injured cells promotes SIRS in AP by binding with P2 × 7 receptors to promote the production of TNF-α and chemokines [135]. Leukotriene B4 (LTB4) is a forceful chemoattractant and inflammatory mediator. Li et al. showed that substance P (SP) regulates the production of LTB4 through the PKCα/MAPK pathway, which aggravates SAP-associated ALI via promoting the reverse transendothelial cell migration (rTEM) of PMN [136].

Put together, SAP is characterized by the continuous development of SIRS and the mortality of SAP is determined by the severity of SIRS. Thus, SIRS is an essential mechanism of SAP-associated ALI promoted by inflammatory mediators released from pancreatitis and intestinal barrier failure (Fig. 3).

5. The endpoint of SAP-associated ALI：ALI/acute respiratory distress syndrome (ARDS)

At the beginning of the article, we mentioned that the lung is one of the most frequently involved organs in SAP-SIRS, and respiratory failure caused by ALI/ARDS is the main cause of early and late death in patients with SAP. During SAP, local inflammation of the pancreas and intestinal barrier failure initiate and amplify SIRS, and then the accumulation of inflammatory mediators and inflammatory cells in the lung damage pulmonary vascular endothelial cells, alveolar epithelial cells, and destroy the lung-gas-blood barrier. With increase in pulmonary vascular permeability, protein-rich fluid overflow into the alveoli and pulmonary interstitium, causing pulmonary edema, diffuse alveolar injury (DAD), and finally ALI/ARDS characterized by hypoxemia (Fig. 4).

5.1. *Endothelial barrier*

Pulmonary vascular endothelial cells (PVECs) are the receptor-effect

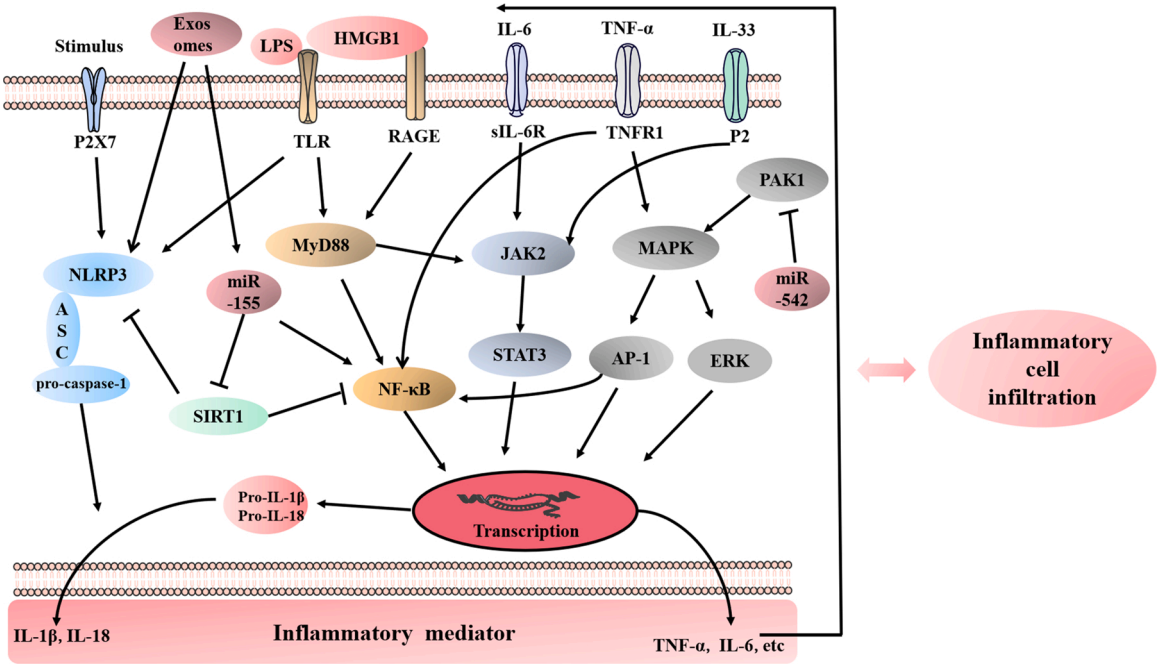

Fig. 3. The hub of SAP-associated ALI. A large number of inflammatory activators(such as endotoxin, HMGB1, and pro-inflammatory factors) activate a variety of intracellular signaling pathways(especially NF- κ B, NLRP3, STAT3, ERK, MAPK and AP-1) by binding to specific receptors, thereby releasing a range of inflammatory mediators and promoting each other with PMN activation and macrophage polarization to form a vicious circle(exosomes and non-coding RNAs may fully involved in this process).

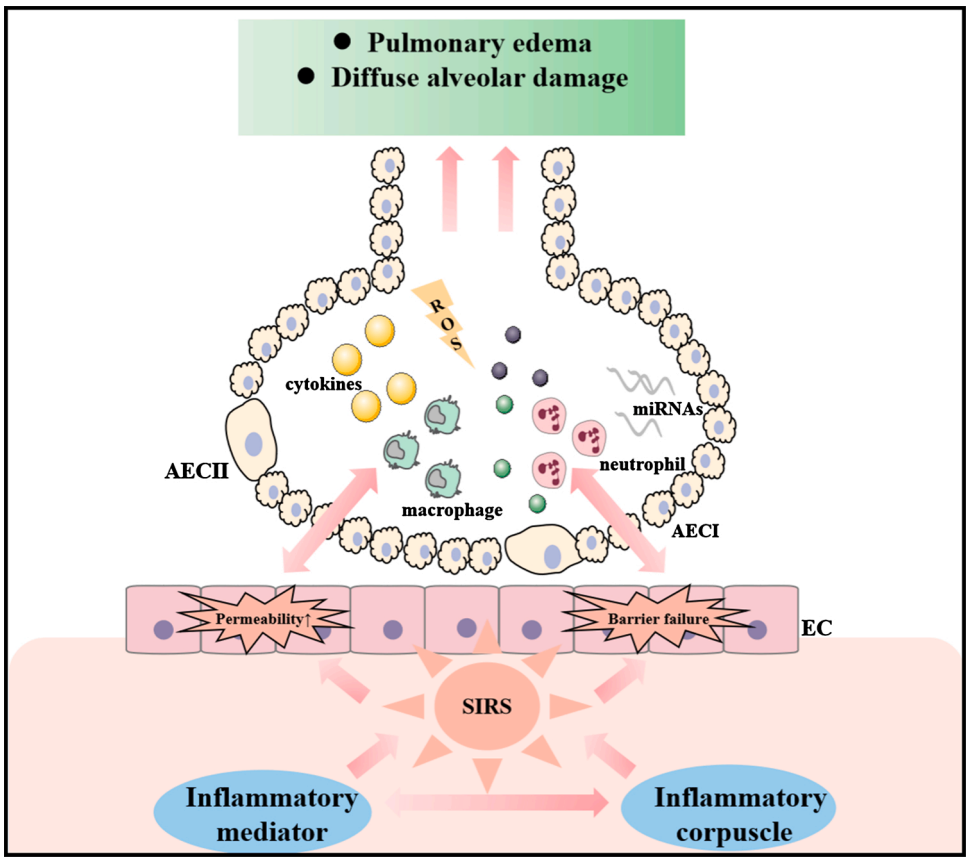

Fig. 4. The endpoint of SAP-associated ALI. The accumulation of inflammatory mediators and inflammatory cells in the lung damages pulmonary vascular endothelial cells and alveolar epithelial cells. With the increase in pulmonary vascular permeability, protein-rich fluid overflowed to the alveoli and pulmonary interstitium, causing pulmonary edema and diffuse alveolar injury (DAD).

barrier between blood and the pulmonary interstitium, which play important roles in regulating pulmonary vascular tension, maintaining vasomotor balance, and controlling the adhesion and metastasis of inflammatory cells. Wang et al. first observed that damage to the PVECs in the SAP-associated ALI model occur prior to other barrier damage. In the early stage of SAP, inflammatory mediators, intestinal PAMPs, and inflammatory cells damage the PVECs and enter the alveoli through the cracks and channels on the endothelial barrier, encouraging the development of ALI [137]. Inflammatory mediators including TNF-α, IL-1β, and HMGB1 can affect the ultrastructure and TJ of PVECs, resulting in the increase of endothelial permeability and the formation of cell gaps [138,139].Additionally, PVECs can form a pro-inflammatory phenotype and release copious amount of inflammatory mediators which further promote the production of ROS, decrease anti-inflammatory mediators and accumulation of inflammatory cells, thus resulting in progressive damage of the endothelial barrier [140]. In the second section of this article, we mentioned that SAP often causes intestinal barrier failure, and a large number of PAMPs amplify the inflammatory cascade through systemic and lymphatic circulations, thus establishing connections with the lung. Endotoxin specifically activates PVECs, resulting in the activation of specific receptors (TLRs, P2 × 7) and secretion of inflammatory mediators [141]. Furthermore, the accumulation of endotoxin in the lung can change the biomechanical properties of the polymorphonuclear leukocytes (PMN), decrease their deformability, and trap them in the capillaries. The inflammatory mediators produced by activated PVECs in turn promote the activation of PMN, and also regulate the release of cytotoxic substances such as proteolytic enzymes, granzymes, ROS, cytokines, chemokines, and neutrophil extracellular traps (NETs) [142]. The mechanism of SAP-associated ALI mainly include the following aspects : Early pro-inflammatory mediators up-regulate the expression of ICAM-1, platelet EC adhesion molecule-1 (PECAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin, thereby promoting the adhesion of PMN. As mentioned earlier, IL-18, an early substitute index of SAP organ failure, has been shown to activate PMN and also induce their accumulation in the lung [143] ; ②Macrophage inflammatory protein-2 (MIP-2), monocyte chemokine protein-1 (MCP-1), IL-8 (CXCL-8), chemokine receptor 3 (CXCR3) and CXCL4 are the most important endogenous chemokines for PMN activation and adhesion in SAP. The inflammatory network constructed by chemokines, pro-inflammatory factors and adhesion molecules play a crucial role in promoting massive infiltration of PMN in the lung [144–148] ; ③After the activation of PMNs, massive release of free radicals (ROS, superoxide anion) and arachidonic acid directly damage the structure of the PVECs and destroy the endothelial barrier ; ④A range of responses between PVECs and inflammatory mediators, endotoxin and PMN disrupt the endothelial barrier, principally by causing the release of PAF, ET-1, and iNOS which destroys the PVECs tight junction and overdilate blood vessels [140]. Recently, studies have revealed that pyroptosis of PVECs plays a fundamental role in ALI. Cheng et al. found that inflammatory activators (endotoxin, IFN) can trigger Caspase-11-dependent PVECs pyroptosis, destroying the endothelial barrier, and thus contributing to the occurrence of pulmonary edema and ALI [149]. In the previous section, we mentioned that SOCE is an important mechanism for regulating calcium influx. Wang et al. showed that SOCE plays a key role in SAP associated ALI, and silencing SOCE can protect SAP-associated ALI by inhibiting mitochondrial-related apoptosis of PMVECs [150]. Cold-induced RNA binding protein (CIRP) is a newly discovered DAMP. It has been noted that increased serum CIRP concentrations reflect the severity and prognosis of SAP [151]. Yang et al. found that CIRP induces

Caspase-1-mediated EC pyroptosis via the activation of NLRP3, resulting in endothelial dysfunction and permeability changes [152]. Unfortunately, these role of CIRP haven't been validated in the SAP-associated ALI model. Therefore, endothelial barrier dysfunction in lung tissues serve as the primary pathological basis of SAP-associated ALI.

5.2. Epithelial barrier

The alveolar epithelial barrier composes of two types of alveolar epithelial cells (AECs): type I and type II. AECs ensures an intact anatomical alveoli structure and a functional gaseous exchange barrier, for alveolar fluid clearance (ENaC, Na+-K+-ATP enzymes), and has the ability to secrete alveolar pulmonary surfactant (PS) [153]. AECIs, which are large flat cells, account for about 90–95 % of the alveolar surface area. The AECIIs are the main component of the alveolar epithelial cells that synthesize and release PS, clear alveolar fluid, and exert the function of cell proliferation and differentiation [154]. PS consists principally of dipalmitoyl phosphatidylcholine (DPPC) and SP ; any factors that affect its production, secretion, and metabolism may cause catastrophic consequences to the lung. Previous reports indicate that the expression of SP-A is negatively correlated with the extent of lung injury in SAP [155]. Zhu et al. found that serum SP-A levels may help to distinguish SAP-associated ARDS from other groups [156]. Yu et al. showed that SP-D dampens SAP-associated ALI by inhibiting the activation of NLRP3 and NF-κB [157]. The mechanism of alveolar collapse caused by the hydrolysis of DPPC by PLA2 during SAP is well recognized. In reality, the impact of SAP on PS is overwhelming. By binding to TLR2 or TLR4 receptors on AECII cells and alveolar macrophages, endotoxins trigger the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), which interfers with the components of the PS [158]. AECIIs maintain alveolar fluid levels through epithelial sodium channel (ENaC) and Na^{+}–K^{+} ATPase. Pre-B-cell colony-enhancing factor (PBEF) is an adipose cytokine secreted by visceral adipocytes. FK866 (a competitive inhibitor of PBEF) promotes PMN apoptosis through mitochondria and death receptor apoptosis pathway, thus protecting SAP-associated ALI [159]. Xu et al. showed that PBEF inhibits the sodium-water transport system by activating ERK and inhibiting the AKT signaling [160]. Furthermore, the normal expression of TJs are crucial for epithelial barrier; and a range of studies have found that some Claudin proteins (Claudin-18, Claudin-4) in addition to maintaining barrier permeability also control lung cell phenotype and inflammation [161]. Xia et al. found that the mRNA and protein expression levels of Claudin-4, Claudin-5, and Occludin in lung tissue decrease significantly in the SAP model [36]. Finally, a series of reactions in SAP-associated ALI, such as endotoxin, inflammatory mediators, IFN-γ, matrix metalloproteinases, microRNAs, and ROS, directly or indirectly alter the expression of TJs, thus affecting the permeability of the lungs epithelial barrier [162].

6. Valuable treatment strategies for SAP-associated ALI

In recent years, improving intestinal barrier function has been a focus on the treatment of SAP. It is gratifying that enteral nutrition is beneficial in SAP. Wereszczynska-Siemiatkowska et al. suggested that early enteral nutrition is superior to delayed enteral nutrition for the prevention of respiratory failure and death in acute pancreatitis [163]. Short-peptide-based enteral nutrition (SPEN) can maintain mechanical barrier function and mucosal immunity, reduce mucosal inflammation, and protect symbiotic bacterial translocation after SAP [164]. The benefits of early enteral nutrition in maintaining intestinal barrier function in visceral fat obesity (VFO) patients have also been demonstrated [165]. Given the above studies, we recommend that patients with SAP receive enteral nutrition as soon as possible. So far, studies on the application of probiotics to SAP are fast emerging, However, most clinical trials have shown that probiotics does not prevent against intestinal barrier damage, endotoxemia, and organ failure in SAP [166, 167]. Only few studies showed that a specific combination of probiotic strains can reduce bacterial translocation during SAP [168]. Given the extensive effect of intestinal flora imbalance in SAP, we believe that probiotic therapy is still a potential valuable direction for clinical treatment and research of SAP.

The inflammatory cascade is the key link to SAP-associated ALI. Regulating inflammatory response seems to be the most valuable treatment strategy. In the previous section, we evaluated the central role of P38MAPK in regulating the release of inflammatory mediators in SAP. In a randomized, double-blind study (77 patients), Christie et al. found that dilmapimod (a novel p38 MAPK inhibitor) can be used to prevent the occurrence of acute respiratory distress syndrome [169]. This result provides a potential research direction. Blood purification can remove and regulate inflammatory mediators in circulation, and it is widely used in clinical regulation of inflammatory mediators release and rescue of critically ill patients. In a small sample study (64 patients), Guo et al. found that early blood purification therapy can remove excess inflammatory mediators and improve immune function, thereby reducing the occurrence of MODS and ARDS [170]. Also, continuous blood purification therapy can effectively improve intestinal barrier dysfunction, by down-regulating iNOS through removing excessive inflammatory mediators [171]. Based on the role of blood purification therapy in regulating inflammatory response, we recommend early and continuous blood purification therapy in patients with SAP associated ALI.

In addition, some potential treatments have also been revealed by researchers. Peng et al. found that thoracic duct ligation reduces PMN infiltration and TNF-α release in acute hemorrhagic necrotizing pancreatitis (AHNP), but aggravates intestinal injury and pancreatitis. However, thoracic catheter drainage can reduce lung injury, intestinal injury, and pancreatitis in AHNP rats [172]. Measures such as thoracic catheter drainage may play a positive role in SAP and related organ injury, but a large number of clinical data are still needed to support these findings.

7. Conclusion

In conclusion, the "P-I-I/E–L pathway" is a complex mechanism involving multi-mediators, multi-pathways, and multiple organs, and is one of the explanations for the increased mortality of SAP patients. Cholelithiasis, alcohol, and hypertriglyceridemia cause abnormal activation of pancreatic trypsin, calcium overload in acinar cells, oxidative stress, activation of NF-κB, and dysfunction of related organelles, leading to acinar cell necrosis and early occurrence of SIRS. Subsequently, intestinal mucosal ischemia and hypoxia results from local pancreatic injury and microcirculatory disturbance, leading to intestinal barrier failure. Bacteria, endotoxin, and related toxic factors entered the lung via the lymphatic channels and systemic circulation ; Finally, a large number of inflammatory activators (such as endotoxin, HMGB1, and pro-inflammatory factors) activate a variety of intracellular signaling pathways (especially NF-κB, NLRP3, STAT3, ERK, MAPK and AP-1) by binding to specific receptors, thereby releasing a range of inflammatory mediators which promote each other, with PMN activation and macrophage polarization in a vicious circle (exosomes and non-coding RNAs are fully involved in this process), leading to lung-gas-blood barrier damage and DAD. This explains the specific pathological link of the development of SAP from early inflammation to intestinal injury, SIRS, and ALI, and is named the "P-I-I/E–L pathway" and proposed in this paper. This pathway reflects the characteristics of multi-link and multi-level participation in the pathogenesis of SAP and provides some feasible ideas and suggestions for multi-target treatment of SAP-associated ALI (inhibition of cellular and tissue oxidative stress, stabilization of intracellular calcium homeostasis, restoration of pancreatic blood flow, regulation of intestinal flora, restoration of intestinal barrier function, inhibition of inflammatory pathway activation and regulation of inflammatory cell apoptosis).

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Declaration of Competing Interest

The authors report no declarations of interest.

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