Advances in the Pathogenesis of Severe Acute Pancreatitis

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Abstract Severe acute pancreatitis (SAP), the most severe and prognostically poorest form of acute pancreatitis (AP), is characterized by rapid onset, swift disease progression, diverse complications, and a high mortality rate. In recent years, influenced by changes in dietary structure and the rising prevalence of metabolic diseases, the incidence of SAP has shown a continuous increasing trend. This paper reviews and summarizes the main pathogenic mechanisms and recent research progress on SAP, hoping to provide a reference for early disease identification, risk assessment, and targeted therapy.

Key words Severe acute pancreatitis; Molecular mechanism; Cellular inflammation; Microcirculatory disturbance

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Acute pancreatitis (AP) is a disease characterized by local inflammatory response of the pancreas caused by various etiologies, which may also involve multiple organs throughout the body. According to the *Revised Atlanta Classification* (2012), AP is categorized into mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis (SAP). SAP accounts for approximately 20% of all AP cases, but its mortality rate is significantly higher than that of mild cases[1-2]. The main cause of early death in SAP is persistent organ failure, while secondary infection of pancreatic necrosis is an important factor contributing to late death[3]. The pathogenesis of SAP is complex and has not yet been fully elucidated. Current research suggests that its core pathological processes include damage to pancreatic acinar cells, abnormal activation of pancreatic enzymes, inflammatory cascade reactions, and systemic immune imbalance. It is noted that local injury of the pancreas can further induce systemic inflammatory reaction, leading to vascular endothelial injury, capillary leakage and multiple organ failure[4-5]. In recent years, with advances in molecular biology, immunology, and cell biology research, the understanding of SAP has gradually deepened. This paper reviews the research progress on the pathogenesis of SAP, focusing on abnormal activation of pancreatic enzymes, inflammatory response, mechanisms of cell injury, microcirculatory disturbances, and abnormal immune regulation.

Abnormal Activation of Pancreatic Enzymes and Pancreatic Autodigestion

Abnormal activation of pancreatic enzymes is considered a core event in the pathogenesis of acute pancreatitis[6]. Under normal conditions, the digestive enzymes secreted by the pancreas exist in the form of zymogens, such as trypsinogen and prolipase, which are activated only after entering the duodenum. However, under certain pathological conditions, pancreatic enzymes can be prematurely activated within pancreatic acinar cells, leading to autodigestion of pancreatic tissue. Abnormal activation of trypsinogen is thought to be a key initiating step[7]. Activated trypsin can not only directly damage pancreatic tissue, but also activate other digestive enzymes (e.g., elastase and phospholipase A2), thereby triggering a cascade of tissue injury responses. Moreover, pancreatic enzymes can damage pancreatic blood vessels, leading to local tissue hemorrhage, necrosis, and edema[8]. Recent studies have shown that abnormal activation of pancreatic enzymes is closely associated with various intracellular processes. Petersen *et al.*[9] found that when intracellular Ca^{2+} level rises abnormally and exceeds the normal spatiotemporal regulatory range, it can lead to the secretion dysfunction of acinar cells, promoting premature activation of pancreatic enzymes and further inducing microcirculatory dysfunction, oxidative stress, and mitochondrial damage. The biogenesis and maturation of autophagosomes are closely related to the physiological functions of the endoplasmic reticulum (ER). The ER is generally considered an important source for the formation of autophagosomal membrane structures. When the load of protein synthesis exceeds the folding capacity of the ER, unfolded or misfolded proteins accumulate in the ER, inducing ER stress. Such a stress state may affect the synthesis of autophagy-related membrane proteins, thereby interfering with the autophagic process. This change may promote the occurrence and progression of AP to a certain extent[10]. This theory has been validated in animal experiments. He *et al.* found that certain compounds can maintain the stable supply function of the ER during autophagic membrane formation. For example, 4-phenylbutyrate significantly alleviates ER stress and helps maintain a cellular environment conducive to protein folding in AP models. In addition, impaired autophagic function is considered a downstream event of mitochondrial dysfunction, a process closely associated with ER stress

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and lipid metabolism disorders, and plays an important role in promoting the occurrence and development of AP. Gyorgy Biczo *et al.* [11] established AP mouse models using L-arginine, cerulein, and bile acids, and assessed the degree of pancreatitis, mitochondrial function, autophagy level, ER stress, and lipid metabolism in pancreatic tissue, acinar cells, and isolated mitochondria. The results indicated that mitochondrial dysfunction plays a central role in the development and progression of AP, and impaired autophagic function is considered as an important downstream effect.

Inflammatory Response and Inflammatory Cascade

The inflammatory response plays a critical role in the development and progression of SAP. After pancreatic injury, a large number of inflammatory mediators and cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (IL-1β, IL-6), are released. These factors further activate immune cells and continuously amplify the inflammatory response[12]. The Toll-like receptor 4 (TLR4) and nuclear factor-κB (NF-κB) signaling pathways play important roles in the inflammatory process of SAP. They participate in the regulation of the onset of inflammation and play key roles in disease progression[13]. Previous studies have shown that Zhang *et al.* [14] established SAP mouse models using cerulein plus lipopolysaccharide (LPS) in wild-type mice, TLR4 knockout mice, and TLR4-overexpressing cells. Combined with fecal microbiota transplantation experiments and the detection of relevant indicators, they found that glycyrrhetinic acid (GAA) alleviated SAP by inhibiting the TLR4 signaling pathway, reducing inflammation, remodeling the gut microbiota, and repairing the intestinal barrier. Once TLR4 is activated, it initiates intracellular signaling, induces NF-κB activation, and subsequently promotes the expression and release of various inflammatory cytokines, thereby exacerbating pancreatic and systemic inflammatory responses. Guo *et al.* [15] established a rat model of SAP and measured serum amylase and TNF-α levels, brain water content, blood-brain barrier permeability, matrix metalloproteinase-9 (MMP-9) expression, ERK/NF-κB pathway phosphorylation, and the expression of tight junction proteins (ZO-1, Claudin-5). The results showed that irisin inhibited the phosphorylation of the ERK/NF-κB signaling axis, reduced MMP-9 expression, and thereby alleviated tight junction degradation, thereby ameliorating blood-brain barrier dysfunction induced by SAP. As the inflammatory response progresses, it can lead to systemic inflammatory response syndrome (SIRS)[16]. When the inflammatory response becomes uncontrolled, large amounts of inflammatory mediators enter the bloodstream, triggering a systemic inflammatory reaction that causes vasodilation, increased capillary permeability, and inadequate organ perfusion. In severe cases, this can progress to multiple organ failure. In addition, neutrophils also play an important role in the inflammatory response of SAP[17-18]. Using two mouse models (taurocholate infusion into the pancreatic duct and intraperitoneal injection of L-arginine) and DNase I intervention combined with *in-vivo* and *in-vitro* experiments, Mohammed Merza *et al.* [19] found that neutrophil extracellular traps (NETs) formed in the pancreas of AP and activated acinar cells via histones, exacerbating inflammatory injury in both the pancreas and the lungs. Clearance of NETs alleviated this injury, and the plasma NET level in SAP patients were significantly elevated.

Mechanisms of Cell Injury and Programmed Cell Death

Apoptosis and necrosis

In AP, the main modes of pancreatic acinar cell death include apoptosis and necrosis[20]. Apoptosis is a tightly regulated form of programmed cell death that causes relatively little damage to surrounding tissues. In contrast, necrosis releases large amounts of inflammatory mediators, thereby inducing or exacerbating the inflammatory response. In SAP, necrosis is more common, and its extent is closely correlated with disease severity[21]. Xu *et al.* [22] found that galangin exerted a protective effect through the NRF2/Srxn1 antioxidant pathway and the NF-κB inflammatory pathway, reducing oxidative stress, inhibiting inflammatory responses and apoptosis, and thereby alleviating pancreatic injury in acute pancreatitis. Studies suggests that galangin may represent a safe and promising therapeutic strategy for AP. In AP, pancreatic acinar cells are exposed to various stimuli, including abnormal activation of pancreatic enzymes, oxidative stress, and calcium imbalance, which can lead to cell death. Among these, necrosis is the predominant form of death in AP. Jia *et al.* [23] established a rat model of acute necrotizing pancreatitis induced by sodium taurocholate and pretreated the animals with the poly(ADP-ribose) polymerase (PARP) inhibitor 3-aminobenzamide to evaluate adrenal injury and functional changes. The results showed that acute necrotizing pancreatitis in rats led to PARP overactivation, enhanced inflammatory responses, and impaired adrenal function. Treatment with 3-aminobenzamide inhibited the inflammatory response, reduced adrenal injury, and improved adrenal function. Therefore, PARP overactivation is involved in the development of adrenal dysfunction associated with acute necrotizing pancreatitis, and inhibition of PARP may have potential therapeutic value.

Autophagy dysregulation

Autophagy is an important cellular mechanism for clearing damaged organelles and proteins[24]. Under physiological conditions, autophagy removes damaged organelles and abnormal proteins, helping to maintain cellular homeostasis. In AP, the autophagic process is often inhibited or dysfunctional, leading to the accumulation of autophagosomes and lysosomal dysfunction. These changes promote the abnormal activation of pancreatic enzymes and exacerbate cell injury[25]. Li *et al.* [26] established a rat model of AP induced by sodium taurocholate *in vitro*. They found that emodin alleviated pancreatic tissue injury, reduced autophagosome formation, and decreased the expression levels of autophagy-related proteins such as LC3 and p62. These findings suggest that

emodin may attenuate AP by inhibiting abnormal autophagic responses.

Pyroptosis

Pyroptosis is a form of inflammatory programmed cell death primarily mediated by inflammasomes[27]. Studies have shown that pyroptosis plays an important role in the development and progression of acute pancreatitis. Once activated, inflammasomes promote the release of various inflammatory factors, thereby exacerbating the local inflammatory response in the pancreas and further leading to distant organ injury[28]. Erhan Sahin *et al.* [29] established a cerulein-induced rat model of acute pancreatitis, and found that β-hydroxybutyrate (BHB) alleviated pancreatic tissue injury and inhibited the expression of the NLRP3 inflammasome and related inflammatory factors, suggesting that BHB may ameliorate acute pancreatitis by suppressing inflammasome-mediated pyroptosis.

Microcirculatory Disturbance and Vascular Endothelial Injury

Microcirculatory disturbance is one of the important pathological features of SAP. The pancreatic inflammatory response can cause vascular endothelial injury, vasoconstriction, and microthrombus formation, leading to local pancreatic ischemia and tissue necrosis[30]. During the course of SAP, large amounts of inflammatory mediators such as platelet-activating factor, nitric oxide, bradykinin, and endothelin are released. These substances disrupt the vascular endothelial barrier, increase capillary permeability, and result in capillary leak syndrome[31-32]. Capillary leakage leads to plasma protein extravasation and tissue edema, further exacerbating injury to the pancreas and surrounding tissues. Meanwhile, reduced blood volume and inadequate tissue perfusion can result in multiple organ dysfunction. In addition, intra-abdominal hypertension and abdominal compartment syndrome are common complications of SAP, which can further aggravate organ ischemia and functional failure[33-34].

Immune Imbalance and Systemic Inflammatory Response

SAP is not only a local inflammatory disease, but also a condition characterized by systemic immune response imbalance[35]. In the early stage of the disease, the body often exhibits a pronounced excessive inflammatory response, with the release of large amounts of inflammatory cytokines, forming a "cytokine storm". With the occurrence and development of the disease, some patients can gradually turn to immunosuppression, which is mainly manifested in the decline of immune cell function and the increase of infection risk. This transition from excessive inflammatory activation to immunosuppression is considered one of the important mechanisms underlying infectious complications in SAP[36]. In addition, macrophages, T lymphocytes, and neutrophils also play significant roles in the immune response of SAP[37-38]. The interactions among immune cells form a complex inflammatory network that exerts a substantial impact on the occurrence and development of the disease.

Pathogenesis Related to Different Etiologies

Common causes of AP include biliary stones, alcohol consumption, hyperlipidemia, and drugs[39-40]. Among these, biliary stones and alcohol are the most frequent causes, while the incidence of hyperlipidemia has significantly increased in recent years[40]. The mechanisms by which different etiologies induce acute pancreatitis exhibit certain differences. The following section describes the common types, including biliary and alcoholic pancreatitis.

Biliary pancreatitis

Obstruction of the pancreatic duct by gallstones can block the outflow of pancreatic juice, leading to increased pressure within the pancreatic duct and abnormal activation of pancreatic enzymes. In Western countries, gallstones are considered one of the most common causes of AP, accounting for approximately 40% of cases[41]. It is currently believed that biliary pancreatitis is primarily associated with the migration of gallstones. Gallstones can pass from the gallbladder through the cystic duct into the common bile duct and become impacted at the junction of the pancreatic and bile ducts or the ampulla of Vater, leading to biliopancreatic duct obstruction and impaired outflow of pancreatic juice. The local inflammatory response caused by the passage of stones through the ampulla, transient ampullary obstruction, and reflux of bile into the pancreatic duct are considered important pathological mechanisms by which gallstones induce acute pancreatitis[42].

Alcoholic pancreatitis

Alcohol can directly injure pancreatic acinar cells, and affect pancreatic juice secretion and pancreatic duct patency, thus promoting pancreatic enzyme activation[43]. Alcoholic pancreatitis is one of the important complications resulting from long-term heavy alcohol consumption. As alcohol intake increases, the risk of developing pancreatitis also rises, indicating that alcohol exerts a dose-dependent toxic effect on the pancreas. However, only some long-term drinkers in clinic eventually develop pancreatitis, indicating that its occurrence often needs the participation of other inducing factors. Previous studies have shown that alcohol is metabolized in the pancreas through both oxidative and non-oxidative pathways, producing a variety of metabolites. These substances can alter the structure and function of pancreatic acinar cells and promote the premature and abnormal activation of intracellular digestive enzymes, thereby increasing the likelihood of autodigestion and damage to pancreatic tissue[44].

Hyperlipidemic pancreatitis

Hyperlipidemic pancreatitis is primarily associated with hypertriglyceridemia and is one of the important causes of acute pancreatitis, accounting for approximately 1% – 10% of all cases[45]. A marked elevation in serum triglyceride levels (typically ≥11.3 mmol/L) significantly increases the risk of developing acute pancreatitis[46]. The pathogenesis of hyperlipidemic pancreatitis has not yet been fully elucidated. However, it is generally believed to be related to the toxic effects of free fatty acids and pancreatic mi-

crocirculatory disturbances[47]. Elevated triglycerides are hydrolyzed by pancreatic lipase within the pancreas, generating large amounts of free fatty acids. The local accumulation of these fatty acids exerts toxic effects on pancreatic acinar cells and vascular endothelial cells, thereby triggering an inflammatory response. Meanwhile, the marked increase in chylomicrons raises blood viscosity and causes pancreatic microcirculatory disturbances, leading to pancreatic ischemia and further exacerbating tissue injury. These changes promote the abnormal activation of pancreatic enzymes and ultimately induce acute pancreatitis[48].

Future Research Directions

Although research on the pathogenesis of SAP has deepened in recent years, many aspects of its specific pathological processes remain unclear. Future research needs to further focus on the mechanisms of the inflammatory response, immune regulation, and the roles of related cellular signaling pathways in the initiation and progression of pancreatitis. It is also necessary to strengthen the screening and clinical verification of potential biomarkers for early diagnosis in order to improve the ability of early identification and risk assessment of diseases. Meanwhile, targeted therapy research can be carried out around inflammatory reaction and immune imbalance, combined with comprehensive intervention measures aimed at protecting multiple organ functions. These approaches will help to provide new theoretical basis and intervention means for the clinical treatment of SAP.

Conclusions

SAP is a complex disease resulting from the interplay of multiple factors. Its pathogenesis involves several pathological processes, including abnormal activation of pancreatic enzymes, amplification of the inflammatory response, cell injury and programmed cell death, microcirculatory disturbances, and immune dysfunction. With the development of molecular biology and immunology technology, the medical research on the pathogenesis of SAP has continuously deepened, and certain progress has been made, leading to a clearer understanding of its pathological mechanisms. However, effective targeted therapeutic approaches are still lacking in clinical practice, and the mortality rate of SAP patients remains high. In the future, it is necessary to continue to study its molecular regulatory mechanism and find new potential therapeutic targets, so as to improve treatment effect and patient prognosis.

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