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Review Article

Pathogenesis of Acute Pancreatitis

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Abstract

Acute pancreatitis is an acute inflammation of the exocrine pancreas and is considered a common and severe disease. The most common etiological factors are excessive alcohol consumption and gallstones. The disease has a sudden onset and may rapidly progress to a severe and potentially life-threatening condition. Treatment of acute pancreatitis is primarily conservative and largely based on supportive care and to date, no specific targeted pharmacological therapy for acute pancreatitis has been developed.

A better understanding of the pathogenesis of acute pancreatitis may facilitate the identification of key molecular and cellular mechanisms involved in pancreatic inflammation and contribute to the discovery of novel, more specific therapeutic approaches targeting factors that play an important role. This review summarizes current knowledge of the pathogenesis of acute pancreatitis.

Keywords: *Acute Pancreatitis (AP); Pathogenesis; Pancreatic Inflammation; Systemic Inflammatory Response Syndrome (SIRS)*

Introduction

The pancreas is a gland with mixed, exocrine and endocrine functions. Its exocrine component consists predominantly of acinar cells that synthase, store, and secrete digestive enzymes, whereas the endocrine pancreas regulates glucose metabolism through insulin and glucagon. Under physiological conditions, several protective mechanisms, including the synthesis of proteolytic enzymes as inactive zymogens, endogenous trypsin inhibitors, regulated zymogen secretion, and intracellular degradation pathways, prevent premature enzyme activation and pancreatic autodigestion [1].

Acute pancreatitis (AP) is an acute inflammatory disease that is represented with variable clinical presentation, from mild, self-limiting to severe disease associated with potentially fatal complications [1,2]. According to the revised Atlanta classification, AP is morphologically divided in interstitial edematous pancreatitis and necrotizing pancreatitis. Interstitial edematous pancreatitis is generally milder form and it is more frequent, while necrotizing pancreatitis is more severe condition involving necrosis of pancreatic tissue [2]. Based on clinical presentation, AP is further classified as mild characterized by the absence of organ failure and local or systemic complications, moderately severe characterized by transient organ failure lasting less than 48 hours and/or local or systemic complications and severe AP characterized by persistent organ failure lasting more than 48 hours [2,3].

Clinical presentation in most cases includes acute, severe epigastric pain, frequently spreads towards the back, and in most cases is accompanied by nausea and vomiting [3]. In severe cases, a pronounced systemic inflammatory response may lead to circulatory and respiratory dysfunction and multiple organ failure [1,3].

The reported incidence of AP varies considerably among populations and has increased over recent decades. Gallstones and excessive alcohol consumption remain the two major etiological factors. Other causes, like hypercalcemia, hypertriglyceridemia, different medications, genetic factors, abdominal trauma, vascular disorders, and iatrogenic injury following endoscopic retrograde cholangiopancreatography (ERCP) [1,3].

Common causes	Less common causes	Consider in recurrent AP
Gallstones	Vasculitis Thrombosis	Pancreatic/biliary duct disorders
Alcohol	Pancreatic ischemia	Medications Alcohol
Hypertriglyceridemia	Connective tissue diseases	IPMN
ERCP Medications	Pancreatic tumors Hypercalcemia	Hereditary pancreatitis
Trauma Postoperative	Renal insufficiency	Cystic fibrosis
	Infections (Mumps, CMV, parasites, coxsackievirus)	Autoimmune Idiopathic

Table 1: *Major causes of acute pancreatitis.*

The diagnosis of acute pancreatitis is based on clinical presentation and laboratory findings and requires at least two of three criteria to be present: typical abdominal pain, serum amylase and/or lipase levels at least three times higher than normal, and imaging findings that support acute pancreatitis [2,3]. Management is primarily supportive and includes fluid resuscitation, pain control, and early oral or enteral nutrition, while endoscopic, radiological, or surgical interventions are reserved for selected patients with biliary obstruction, cholangitis, infected necrosis, or other complications [3,4].

Despite advances in supportive and intensive care, specific pharmacological treatment targeting the underlying mechanisms of AP remains limited. A better understanding of responsible for pancreatic injury and the consequential inflammatory response is therefore essential for identifying novel therapeutic targets. In this review we will discuss current insights into the pathogenesis of acute pancreatitis

Main body

Many factors are involved in the pathogenesis of acute pancreatitis, making it highly complex. It is traditionally considered that the process fundamentally begins with the premature activation of trypsin within the pancreas itself, leading to the subsequent activation of other pancreatic enzymes; this results in autodigestion of the pancreas and a consequent inflammatory response that in severe cases may lead to systemic inflammatory response syndrome (SIRS) [5]. More recently it was found that additional cellular mechanisms, including mitochondrial dysfunction, calcium overload, dysregulated autophagy, stress of endoplasmic reticulum, and exosomes, also have important roles in the pathogenesis of acute pancreatitis [6,7].

Role of calcium signaling and mitochondrial dysfunction in acute pancreatitis

Physiologically, cholecystokinin (CCK) induces release of calcium ions from the endoplasmic reticulum of pancreatic acinar cells trough activation of inositol trisphosphate receptor (IP3R). Released calcium stimulates the mitochondria to produce adenosine triphosphate (ATP), and promotes digestive enzyme secretion [6,7]. In pathological conditions in which acinar cells are under the influence of an increased amount of CCK, alcohol or bile acids, there is an excessive accumulation of calcium in the cell, representing an important early event in acute pancreatitis [6,7]. Consequent Ca^{2+} deficiency in the ER activates calcium release-activated calcium channel protein 1 (ORAI1), causing influx of extracellular Ca^{2+} and further accumulation of intracellular Ca^{2+} (Figure 1). Excessive mitochondrial Ca^{2+} uptake subsequently impairs mitochondrial function and ATP production [6-8].

ATP depletion further impairs Ca^{2+} homeostasis by affecting ATP-dependent Ca^{2+} pumps, particularly the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and plasma membrane Ca^{2+}-ATPase (PMCA), thereby leading to a vicious cycle of Ca^{2+} overload, mitochondrial dysfunction, and energy depletion (Figure 1) [7,8].

Ca^{2+} overload leads to premature trypsinogen activation and autodigestion of pancreas. Mitochondrial dysfunction also contributes to impaired autophagy, oxidative stress, and release of pro-inflammatory cytokines. Damaged acinar cells produce and secrete molecules that are associated with cellular damage, such as heat shock proteins (HSP), and similar substances that then activate various pro-inflammatory signaling pathways that can turn local inflammation into systemic [7,8].

Premature trypsinogen activation in acute pancreatitis

Intrapancreatic, premature activation of trypsinogen has been considered as a key early event in the pathogenesis of acute pancreatitis. Under physiological conditions, trypsinogen is an inactive zymogen and is activated to trypsin only after reaching the small intestine. Several mechanisms, including endogenous trypsin inhibitors, regulated apical exocytosis of zymogen granules, and intracellular degradation pathways, prevent inappropriate activation within the pancreas [7,9].

Different factors, including bile acids and alcohol disrupt normal cell trafficking and secretion, promoting the accumulation of lysosomal and pancreatic enzymes in intracellular compartments and their pathological basolateral secretion in interstitium (Figure 1). Cathepsin B (CTSB), a lysosomal protease, can activate trypsinogen within these compartments, while activated trypsin can subsequently promote activation of additional digestive proenzymes, contributing to acinar cell injury and pancreatic inflammation [7,9,10]. Trypsin causes the rupture of lysosomal membranes and the consequent release of cytochrome c from mitochondria, which activates caspase-3 and drives the pancreatic acinar cell into apoptosis. Extensive research is being conducted on trypsinogen activation, and although many mechanisms are understood, there is still room for further progress [10-15].

Role of NF-κB activation in pancreatic acinar cells

Numerous studies have led to the conclusion that the activation of the nuclear factor kappa B (NF-κB) during acute pancreatitis plays a significant role in its course and manifestation and can be independent of premature trypsinogen activation [11,12]. Different studies have shown that excessive NF-κB activation is associated with more severe clinical presentation of acute pancreatitis.

NF-κB signaling can be activated by different stimuli also involved in acute pancreatitis, such as Ca^{2+} overload and heat shock proteins (Figure 1). Activation of the IκB kinase (IKK) complex promotes phosphorylation and degradation of inhibitor of κB (IκB), allowing NF-κB, particularly the p65/p50 complex, to translocate into the nucleus and regulate the transcription of inflammatory genes and production of inflammatory mediators, such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and IL-8 [12].

Besides acinar cells, NF-κB signaling also occurs in endothelial and infiltrating immune cells, thereby amplifying pancreatic inflammation. Recent evidence has shown that mitochondrial damage and mitochondrial DNA release can activate the cGAS-STING-NF-κB

pathway in acinar cells, providing an additional mechanism of persistent inflammation. From these findings we can conclude that NF-κB represents an important link between early acinar cell injury and systemic disease in severe acute pancreatitis [12,13].

Dysregulation of autophagy in acute pancreatitis

Autophagy is a catabolic cellular process by which cells destroy damaged cellular organelles, unwanted proteins, and lipids. Molecules or organelles are transported to lysosomes and degraded by lysosomal hydrolases. In addition, autophagy can enhance or suppress inflammatory processes by influencing pathogen degradation or antigen presentation, thereby stimulating both innate and adaptive immune responses [14,15].

Increasing evidence indicates that impaired autophagic flux and lysosomal dysfunction are important early events in acute pancreatitis. During the disease, defective autophagosome-lysosome fusion and reduced lysosomal degradation led to the accumulation of autophagic vacuoles, damaged organelles, and protein aggregates. These abnormalities are associated with increased levels of LC3-II and p62/SQSTM1 and reduced expression or function of lysosome-associated membrane protein 2 (LAMP2), an important regulator of autophagosome-lysosome fusion [14-16].

Impaired autophagy also promotes abnormal intracellular trypsinogen activation, mitochondrial dysfunction, endoplasmic reticulum stress, and inflammatory signaling, thereby linking several major pathogenic mechanisms of acute pancreatitis. Experimental deletion of key autophagy-related genes, including ATG5 and ATG7, or disruption of lysosomal proteins such as LAMP2, results in acinar cell injury and spontaneous pancreatitis, further supporting the protective role of intact autophagy in pancreatic homeostasis [14-16]. Impaired or blocked autophagy also leads to the accumulation of damaged mitochondria; these fail to produce sufficient ATP, thereby exacerbating the disruption of the autophagy process and further contributing to damage in acinar cells.

Recent evidence therefore suggests that acute pancreatitis is characterized not simply by increased or decreased autophagy, but primarily by defective autophagic flux and lysosomal degradation. Restoration of functional autophagy and lysosomal homeostasis consequently represents a potential therapeutic strategy for limiting acinar cell injury and inflammation [15,16].

Endoplasmic reticulum stress in the pathogenesis of acute pancreatitis

The endoplasmic reticulum (ER) is a cellular organelle that has a major role in synthesis and folding of proteins. Since acinar pancreatic cells have very high rates of protein synthesis, they are especially prone to ER stress. ER stress can be triggered by accumulation of unfolded or misfolded proteins and that accumulation can be consequence of hypoxia, oxidative stress, alcohol, and Ca^{2+} overload. ER stress then activates the unfolded protein response (UPR) [7,17].

The UPR is mediated by three major ER transmembrane sensors: inositol-requiring enzyme 1α (IRE1α), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6) that are maintained in inactive state in physiological conditions. That inactivation is enabled by their interaction with the molecular chaperone glucose-regulated protein 78 (GRP78/BiP). During ER stress, GRP78 dissociates from these sensors, activating the UPR that tries to restore ER homeostasis [17-20]. The consequences of UPR activation depend on the intensity and duration of ER stress. A transient and controlled UPR is predominantly adaptive and protects pancreatic acinar cells. In contrast, severe or persistent ER stress shifts the response toward inflammation and cell death through pathways involving C/EBP homologous protein (CHOP), c-Jun N-terminal kinase (JNK), nuclear factor-κB (NF-κB), and the NLRP3 inflammasome [18-20]. ER stress also interacts closely with Ca^{2+} dysregulation, mitochondrial dysfunction, and impaired autophagy, creating interconnected mechanisms that amplify acinar cell injury and inflammation.

Experimental models demonstrate early activation of ER stress and UPR during acute pancreatitis, supporting their involvement in disease initiation and progression. Recent evidence therefore suggests that maintaining an adaptive UPR while preventing prolonged maladaptive ER stress may represent a potential therapeutic strategy in acute pancreatitis [18,20].

Role of exosomes in the pathogenesis of acute pancreatitis

Exosomes are small extracellular vesicles, around 30-150 nm in diameter, that can transport molecules between cells and enable intercellular communication. Recent studies indicate that exosome levels are increased in blood of patients with acute pancreatitis (AP) and that exosomes are important mediators of intercellular communication in AP, contributing to the propagation of inflammatory signals from injured pancreatic tissue to immune cells and distant organs [21,22].

During AP, pancreatic acinar cell-derived exosomes can modulate macrophage responses and amplify inflammation. It has been demonstrated that exosomes detected in patients with a mild clinical presentation of acute pancreatitis have no effect on macrophages, whereas those detected in patients with a more pronounced and severe clinical presentation of acute pancreatitis promote activation of the NF-κB transcription factor, expression of TNF-α and IL-1β, and the release of free radicals [25]. Exosomes released during acute pancreatitis are thought to activate alveolar macrophages by shifting their phenotype from M2 to M1, thereby promoting the progression of lung injury in acute pancreatitis. These exosomes may also activate the NLRP3 inflammasome, initiating alveolar macrophage activation and further lung injury as a complication of acute pancreatitis [5]. Recent experimental evidence demonstrated that exosomes released from injured acinar cells promote M1 macrophage polarization and pyroptosis through an exosomal miR-24-3p/MARCH3/NLRP3 signaling axis, directly linking acinar cell injury to inflammasome activation [23]. Exosomes may also reach distant organs, including the lungs, where they activate alveolar macrophages and contribute to acute lung injury associated with severe AP [21,22].

Importantly, the biological effects of exosomes depend on their cellular origin and molecular cargo. While injury-associated exosomes may enhance NF-κB and NLRP3 signaling and promote systemic inflammation, extracellular vesicles derived from mesenchymal stem cells have shown anti-inflammatory and tissue-protective effects in experimental models of AP [22,24]. These findings highlight the dual role of extracellular vesicles as both mediators of disease progression and potential therapeutic agents [22,24].

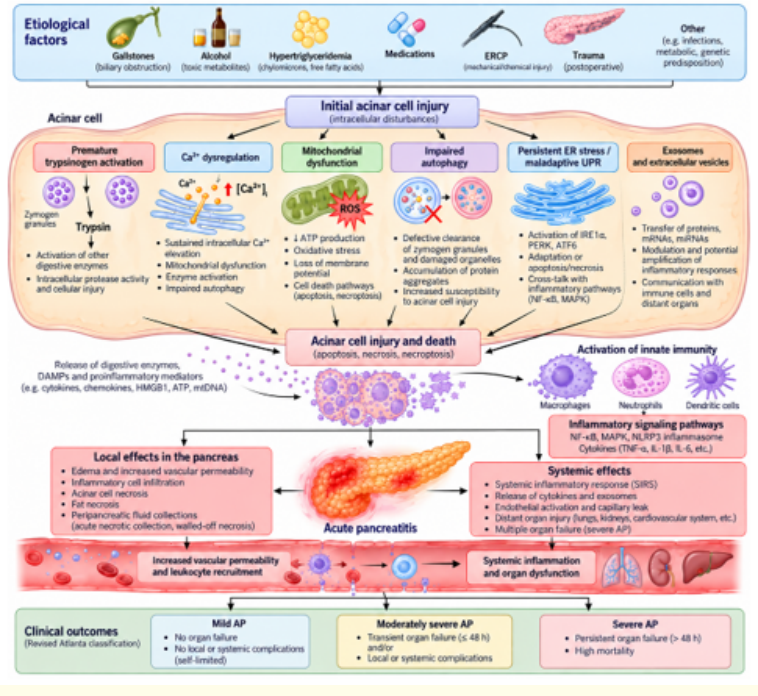

Figure 1: *Schematic overview of the major cellular and molecular mechanisms involved in the pathogenesis of acute pancreatitis, including pathological Ca^{2+} signaling, mitochondrial dysfunction, premature trypsinogen activation, impaired autophagy, endoplasmic reticulum stress, inflammatory signaling, and exosome-mediated intercellular communication [5-8,12,15,16,20,22]. The figure was generated with the assistance of OpenAI ChatGPT based on the scientific concepts and literature reviewed by the authors. The scientific content was reviewed and verified by the authors.*

Future Perspectives

Despite substantial advances in understanding the pathogenesis of acute pancreatitis, the mechanisms that determine disease severity and progression remain incompletely understood. Premature trypsinogen activation is no longer considered the sole pathogenic mechanism, as Ca^{2+} cytoplasmatic accumulation, disturbed autophagy, mitochondrial dysfunction, stress of endoplasmic reticulum, and exosome-mediated intercellular communication form a complex network contributing to acinar cell injury and inflammation.

A major challenge is to develop reliable biomarkers for early prediction of disease severity and complications as well as therapy targets capable of interrupting early pancreatic injury and excessive inflammatory responses. Emerging approaches involving modulation of intracellular Ca^{2+} signaling, mitochondrial and lysosomal function, autophagy, inflammatory pathways, and extracellular vesicle signaling may provide new therapeutic opportunities. A better understanding of these mechanisms may enable new treatment strategies that will improve outcomes in patients with acute pancreatitis.

Conclusion

Acute pancreatitis is a complex inflammatory disease in which initial pancreatic acinar cell injury may progress from local inflammation to systemic inflammatory responses, organ failure, and pancreatic necrosis. Although premature trypsinogen activation remains an important pathogenic event, current evidence indicates that disease development and progression involve multiple interconnected mechanisms, including Ca^{2+} dysregulation, mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, NF-κB-mediated inflammatory signaling, and exosome-mediated intercellular communication. Despite considerable advances, the complex interactions among these mechanisms remain incompletely understood. Further elucidation of the molecular and cellular pathways underlying acute pancreatitis may facilitate the identification of novel biomarkers and therapeutic targets, ultimately enabling more effective targeted treatment and improved patient outcomes.

Declaration of Generative AI Use

Generative artificial intelligence (ChatGPT, OpenAI) was used to create a schematic illustration included in this manuscript. The authors reviewed and verified the scientific accuracy of the figure and take full responsibility for its final content.

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