Review Article

A Review on Acute Pancreatitis: Pathogenesis and Pathophysiology

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ABSTRACT

The specific mechanisms by which various etiological factors trigger an attack remain unclear. It is generally thought. Acute pancreatitis begins in acinar cells. Early acinar cell damage in acute pancreatitis causes a local inflammatory reaction. A significant immune response can cause a systemic immune response syndrome (SIRS). Excessive SIRS causes distant organ damage and multiple organ dysfunction syndrome (MODS). Acute pancreatitis and its associated multiple organ dysfunction syndrome, which leads to death, are mostly caused by inflammatory mediators. Inflammatory mediators such TNF-a, IL-1b, IL-6, IL-8, PAF, IL-10, C5a (Complement component 5a, ICAM-1, and substance play a crucial role, as confirmed by recent investigations. Acute pancreatitis can cause systemic consequences akin to septicaemia, severe burns, and trauma. Classification of acute pancreatitis and their pathologic characteristic and clinical characteristic.

Keywords: MODS- Multiple organ dysfunction syndrome , AP-Acute pancreatitis, TNF-Tumor necrosis factor- α, IL-Interleukin, PAF-Proinflammatory mediator, RER-Rough endoplasmic reticulum, SIRS-Systemic inflammatory response syndrome, CV-Condensing vacuoles.

INTRODUCTION

About 40 cases out of 100 000 people in the United Kingdom have been diagnosed with acute pancreatitis (AP), which is a common disease.[1] A severe attack occurs in 25% of patients, and between 30% and 50% of them will succumb [20% to 50%][2-4]. The primary cause of most cases is biliary disease or excessive alcohol consumption. A systemic inflammatory response syndrome (SIRS) can be caused by a marked local inflammatory reaction at the site of injury. The pathogenesis of pancreatitis and the subsequent immune response seem to have a significant role for cytokine[2-4].

Acute Pancreatitis is a complex condition that can present with mild to severe symptoms. It can be confined in the pancreas, extend to surrounding tissues, or affect other organs[1]. Acute pancreatitis has been challenging to investigate and manage due to its varying clinical severity and morphology since Fitz's description in 1889.[2] Many morphologic words used by gastroenterologists, surgeons, pathologists, and radiologists to characterize disease manifestations have been misinterpreted and misused.

Currently, it is widely accepted that the early release of digestive enzymes into the pancreatic Acinar cells is an important initiating factor that results in the auto-digestion of the pancreas[4-6].

Early event in pancreatitis:

Early events in acute pancreatitis involve the activation of digestive enzymes in the pancreas, leading to inflammation and damage to pancreatic tissue. This can be triggered by various factors such as gallstones, alcohol consumption, or viral infection. The initial phase is characterized by abdominal pain and tenderness, nausea and vomiting, and elevated levels of pancreatic enzymes in the blood. As the condition progresses, complications may arise such as organ failure and infection. Early identification and treatment are crucial to prevent further damage and improve outcomes for patients with acute pancreatitis. The most popular and commonly accepted explanation holds that pancreatitis arises from damage or disruption of the pancreatic acini, allowing trypsin, chymotrypsin, and elastase, the three pancreatic enzymes, to leak into the pancreatic tissue. The tissue is exposed to the spilled enzymes, which causes autodigestion and severe pancreatitis. Trypsin, elastase, and lipase are examples of active proteases that break down tissue and cell membranes, leading to edema, vascular injury, bleeding, and necrosis. Acute pancreatitis and autodigestion are brought on by the tissue's activation of the released enzymes. The activated proteases (trypsin and elastase) and lipase break down tissue and cell membranes, causing edema, vascular damage, hemorrhage and necrosis.[5]

Mechanism of Zymogen Activation:

Several factors contribute to trypsinogen autoactivation, including cleavage by the lysosomal hydrolase cathepsin, decreased activity of the pancreatic trypsin inhibitor, and leaking of zymogens and lysosomes. Enzymes enter the cytoplasm and activate proteases, while zymogens are shunted to membrane-bound compartments with active proteases. Secreted zymogens are then processed by endocytic pathways.[6]

Trypsinogen auto activation:

Trypsinogen autoactivates, hence trypsin-induced activation is the trigger for acute pancreatitis [7]. Recent discoveries suggest that the activation of trypsinogen takes place intracellularly, along the usual secretory pathway, within small intracellular vacuoles containing lysosomal markers but not being lysosomes, and that the release of trypsin into cytoplasm is time-dependent.[8]

The role of calcium:

Additionally, calcium (Ca 2+) can be crucial in acute pancreatitis in its early stages. Both pancreatic duct blockage and cerulein hyperstimulation have been shown to cause pancreatitis. Demonstrated to result in an increase in intracellular Ca 2+ and a disruption of Ca 2+ signaling in acinar cells. This is connected to the intracellular trypsinogen activation events that take place in the early stages of acute pancreatitis and the vacuolization of acinar cells.[9,10,11] Despite the fact that the activation of intracellular trypsinogen is clearly aided by intracellular Ca 2+.Trypsinogen activation was produced by incubating pancreatic acini with the Ca 2+ -ATPase inhibitor thapsigargin.[10] Trypsinogen autoactivation is boosted by the presence of Ca 2+ and necessitates an acidic pH.[12]

Pathophysiology of acute pancreatitis:

Intracellular activation of pancreatic zymogens leading to pancreatic autolysis.

It is currently believed that trypsinogen, a serine protease, is the first enzyme activated.

Subsequently, other predigestive enzymes are degraded and activated.

The pancreas has various mechanisms to prevent intracellular zymogen activation and subsequent autolysis.[13,14,15,16] Calcium may moreover play an imperative part in early AP. Pancreatitis initiated by caerulein hyperstimulation has been appeared to cause a rise in intracellular calcium and a disturbance of acinar cell calcium flagging. This is related with acinar cell vacuolization and the intracellular trypsinogen actuation occasions that happen in early AP.[17,18]

Initiating factor

Acinar Cell Event

Pathologic Changes

Blockage of secretion

Colocalisation of zymogens and Lysosomal enzyme

Zymogen activation

Organelle rupture

Cell Injury

Other organs affected by an excessive inflammatory response include the kidneys and liver. Translocation of endotoxins and bacteria can occur through intestinal wall damage, and prolonged endotoxemia exacerbates the systemic inflammatory response.[19]

TNF-

Tumor necrosis factor- α) (TNF-) is primarily derived from activated macrophages and acts through membrane-bound receptors on cells . Injection of TNF-α in laboratory animals causes a syndrome indistinguishable from septic shock. It is elevated in many diseases that cause shock, including AP and TNF-α is now considered to be one of the major mediators of shock.

Macrophages that have invaded the pancreas show strong reactivity with anti-TNF-α antibodies. An overall increase in both tissue and serum TNF-α concentrations directly correlates with the severity of pancreatic damage and inflammation. Level of TNF- is increase during progress of AP.[20]

IL-6 (INTERLEUKIN-6)

IL-6 levels were reported to be greater in individuals with various main diseases who developed multiple organ failure.[21]

IL-6 plays a crucial role in the acute phase response, since it stimulates the manufacture of acute phase proteins such as CRP from hepatocytes both in vitro and in vivo.[22,23] IL-6 levels are elevated in AP patients and associated with illness severity.[24,25]

IL-6 is a proinflammatory cytokine that is produced by a wide range of cells including monocytes/macrophages, endothelial cells, fibroblast and smooth muscle cells in response to stimulation by endotoxin, IL-1 .[26,27,28,29]

IL-10 (INTRALEUKIN)

IL-10 cannot be measured in serum but is in AP Levels rise significantly within the first 24 hours after an attack and then decline steadily over the next days. In the first 24 hours, serum IL-10- levels are higher in mild AP patients than in severe AP patients. Administration of IL-10 has protective effects in animal models of sepsis.[30-34]

PAF

The proinflammatory mediator (PAF) (1-o-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a low molecular weight phospholipid that acts through specific cell surfaces. receptors have been identified on numerous cells and tissues, including platelets, white blood cells, and cells. Endothelial cells.[26-29] Isolated pancreatic acini have been reported to synthesize his PAF, and concentrations increase within pancreatic tissue during the course of the attack.[35]

PATHOGENESIS OF ACUTE PANCREATITIS

Role of Digestive Enzymes:

Most studies of acute pancreatitis have focused on the process of autolysis of the pancreas by digestive enzymes. In fact, pancreatic acinar cells synthesize and secrete a

variety of digestive enzymes. Most of these enzymes are secreted in the form of inactive zymogens and are not activated under physiological conditions until they reach the duodenum.

There, the brush border enzyme enterokinase activates trypsinogen, and trypsin activates the remaining zymogens.

Until recently, the role of digestive enzymes in the pathogenesis of acute pancreatitis was questioned.

This is because the activated forms of these enzymes were not detected in the glands or bloodstream during the clinical manifestations of the disease.

However, it is recognized that many of these digestive enzymes can rapidly bind to inhibitors in the pancreas or circulating plasma, and measurement of enzyme activity under these conditions can be problematic. As a result, several other strategies have been adopted.

Among them are (a) the use of certain low molecular weight substrates that can also be degraded by enzyme inhibitor complexes; (b) Radioimmunoassay of digestive enzyme amount and enzyme activity.

(c) Quantification of changes in inhibitor levels during pancreatitis.

We hypothesized that the decrease in inhibitor levels reflects activation and consumption of the inhibitor by activated digestive enzymes.

(d) Chromatographic separation of the inhibitor allowing direct measurement of the inhibitor-enzyme complex.

As a result of numerous studies using these approaches, most observers believe that activated digestive enzymes, such as trypsin, chymotrypsin, elastase, and phospholipase, are effective in treating the pancreas, peripancreatic effusions, ascites, and the like in the presence of acute pancreatitis. We concluded that it is indeed present in the circulating fluid.[36-42]

Gallstone Pancreatitis

Most attacks of acute pancreatitis are caused by bile duct stones affected either in the terminal biliopancreatic duct system "father's ampoule" or in the distal biliopancreatic duct system.

Alternatively, it enters the duodenum through the sphincter of Oddi.[1]Three mechanisms by which stone passage/ fecal impaction and pancreatitis may be associated have been suggested.

(a) Impingement of a stone into the ampulla may result in reflux of bile into the pancreatic duct system proximal to the obstruction.

(b) Passage of a stone may cause the sphincteric system to malfunction, allowing duodenal contents to flow back into the pancreatic ductal system.

(c) Ampullary obstruction due to stone impingement or inflammatory response and edema after stone passage can cause pancreatic duct obstruction, and if exocrine secretion continues, pancreatic ductal hypertension.[42]

SYNTHESIS AND TRANSPORT OF DIGESTIVE ENZYME

Ribosomes connected to pancreatic acinar cells' rough endoplasmic reticulum (RER) produce digestive enzymes. The resulting polypeptide chain is lengthened in the RER baths, and after completion, the newly produced protein is transferred to the Golgi complex. There, they are packed into condensing vacuoles (CVs) and develop into zymogen granules (ZGs), which migrate to the luminal cell surface and release their contents into the lumen via exocytosis. The digesting enzyme zymogens are encapsulated in membrane-enclosed organelles (i.e. RER, CV, ZG).[43]

CLASSIFICATION OF ACUTE PANCREATITIS:

Pathologic Characteristics

Acute pancreatitis is an inflammatory condition that can be caused by various reasons. On the basis of the severity pathologic changes, clinical manifestation and laboratory values.

Acute pancreatitis can be characterized as moderate or severe based on pathologic alterations, clinical symptoms, and test results.

This classification is valuable for clinical purposes, however it only covers the end of a complex and changeable spectrum of disease, including transitional stages with clinical and pathologic anomalies.

Clinical Characteristics:

Acute pancreatitis typically causes upper abdominal pain, vomiting, and a range of abdominal symptoms, including moderate tenderness and rebound. Symptoms commonly include fever, tachycardia, and leukocytosis. Elevated pancreatic enzyme levels in blood or urine typically confirm the diagnosis.

Mild acute pancreatitis:

Mild acute pancreatitis is characterized by modest systemic and organ damage. It responds quickly to conservative medical therapy and resolves clinical symptoms and test abnormalities.

Severe acute pancreatitis:

Severe acute pancreatitis is characterized by significant symptoms, physical indications, and test results. Occasionally, flank or periumbilical ecchymosis (Grey-Turner sign or Cullen sign) may occur. Systemic and organ failure can manifest as shock (systolic blood pressure < 90 mm Hg), pulmonary insufficiency (oxygen pressure < 60 mm Hg), renal failure (creatinine level > 2 mg/dL [180 mmol/L] after rehydration), gastrointestinal bleeding, or a combination of these. Metabolic abnormalities, including low serum calcium levels (< 7.5 mg/dL [1.87 mmol/U]) and disseminated intravascular coagulation, may occur.

CONCLUSION

Advancements in understanding the pathophysiology of acute pancreatitis have occurred over time. In acute pancreatitis, trypsinogen activation is a crucial early event that causes acinar cell damage. Inflammatory mediators involve in the acute pancreatitis TNF-a, IL-1b, IL-6, IL-8, PAF, IL-10, C5a (Complement component 5a, ICAM-1. Currently, it is commonly known that the early release of digestive enzymes into the pancreatic Acinar cells is a crucial beginning component in the pancreas' auto-digestion.

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