

# Current concept of pathogenesis of severe acute pancreatitis

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The pathogenesis of severe acute pancreatitis is very complicated. It is a multifactorial as well as multifaceted disease. First of all, the etiologic agents initiate the pancreatic acinar injury by release of pancreatic enzymes and overstimulation of macrophages and neutrophils, then the cytokines and inflammatory mediators are liberated. There is also interaction between neutrophils and endothelial cells producing free radicals, the cytokines cause increasing vascular permeability, activating complement component, resulting in microcirculatory impairment and imbalance of thrombo-fibrinolytic system. Many of these events occur not only in the pancreas itself, but also in the other vital organs and tissues, leading to severe acute pancreatitis and complications. The sequential events are as follows.

## PANCREATIC ACINAR INJURY

### *Pancreatic duct obstruction and bile reflux*

Gallstone incarcerated in the distal common duct or biliary-pancreatic duct common pathway initiates bilereflux, activates pancreatic trypsin, produces acinar injury which is the traditional viewpoint, but is unexplainable in case when biliary and pancreatic ducts open into the duodenum individually and in those so called idiopathic acute pancreatitis. It had been found that 91% of such cases had microlithiasis or biliary sludge as the cause of transient incarceration. In animal experiments, ligation of pancreatic duct can also induce acute pancreatitis without having bile reflux, showing that pancreatic duct obstruction is also an important pathogenetic factor<sup>[1]</sup>. Such microlithiasis could not be disclosed by the conventional cholecystography, but could be shown from the bile taken from the recovered patients. After centrifuged and observed under

microscope, clustered cholesterol crystals, bilirubin and calcium bicarbonate microgranules were found in 67% of cases<sup>[2]</sup>. Many recurrent pancreatitis patients when followed up by ultrasound for 12 months, there were cholesterol crystals and microlithiasis, the biliary sludge and microlithiasis could also be seen in the gallbladder specimens, indicating there had been pancreatic obstruction<sup>[3]</sup>. Pancreatic obstruction caused impedance of pancreatic fluid outflow resulted in elevation of pancreatic pressure and produced pancreatic acinar injury.

### *High fat, high protein diet*

High fat and high aminoacid content in the duodenum can stimulate cholecystokinin (CCK) release, which promotes the acini to secrete enzymes. The zymogen granules located at the fusion of the apical cell membrane dislocate and scatter throughout the cell cytoplasm after stimulation. At this stage, the cells show vacuolation because the zymogen granules have been exocytosed. Alcohol can also sensitize the acini to CCK, activate the intracellular and intraluminal pancreatic enzymes, and initiate the catabolism of intracellular protein under the condition of low pH and ionic changes. Two mechanisms have been proposed to account for the intracellular activation of trypsinogen and the zymogen cascade: trypsinogen autoactivation and trypsinogen activation by the lysosomal enzyme cathepsin B. These are the earliest changes in acute pancreatitis<sup>[4]</sup>, then activated trypsin again activates other pancreatic enzymes, including pancreatic lipase, amylase, chymotrypsin, phospholipase A<sub>2</sub>(PLA<sub>2</sub>), elastase, carboxylase, nucleotidase, etc. which induce autodigestion of the pancreas. In animal experiments, administering CCK or CCK analogue i.e., cerulein into ligated pancreatic duct, can induce edematous pancreatitis; and injecting taurocholic acid into ligated pancreatic duct can cause necrotizing pancreatitis.

### *Alcohol*

Alcohol has deleterious effects on both pancreatic acini and Oddi's sphincter<sup>[5]</sup>. ① It stimulates gastrin secretion and via the cholinergic pathway to stimulate pancreatic secretion, simultaneously, it can cause spasm of Oddi's sphincter, the two in combination can lead to pancreatitis. ② Alcohol

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may change the composition of proteins secreted by the pancreas, resulting in the formation of protein plugs within small pancreatic ductules, this insoluble protein is formerly called stone protein. ③ It increases the amount of lysosomal enzymes and increases trypsinogen/pancreatic trypsinogen inhibitor ratio. ④ Ethanol can change systemic and pancreatic lipid metabolism with accumulation of lipid droplets within the acinar cells, alter membrane fluidity and integrity. ⑤ Ethanol even sensitizes the acinar cells to CCK-stimulated intracellular zymogen proteolysis. In presence of combined-stimulation of CCK and alcohol, it is easier to induce acute pancreatitis.

#### ***Ischemia, decreased perfusion***

Transient ischemia enhances enzymatic degradation of acinar cells which become more vulnerable. Hypotension during bypass surgery, pancreatic atherosclerosis with hyperfunction of sympathetic nervous system in the elderly, in combination with the above factors can result in acute pancreatitis with necrosis. Animal experiments on ligation of pancreatic duct and injecting cerulein or taurocholic acid, with additional clamping of upstream of pancreatic artery, that is the celiac artery and superior mesenteric artery for 40 min, can cause pancreatic necrosis, edema and inflammation.

Based on the above facts, severe acute pancreatitis can be induced by a combination of multifactors, which include pancreatic obstruction with or without bile reflux, high fat, high protein diet (hyperstimulation of CCK), alcohol, and ischemia, this is what we encounter in our clinical practice, these factors interact with one another and result in this disease.

#### **CHANGES AFTER ACINAR INJURY**

##### ***Activation and release of pancreatic enzymes***

Activated trypsin again activates other pancreatic enzymes, among which, chymotrypsin promotes hydrolysis of tryptophan, tyrosine and phenylalanine peptide chain; elastase hydrolyzes elastic fibers of extracellular matrix, promotes spreading of protein degradation; carboxypeptidase A and B and RANase, each acts on the components of pancreatic tissue; pancreatic lipase hydrolyzes the lipids, triglyceride, produces free fatty acid which is toxic to the capillaries, leads to lipoperoxidation; and PLA<sup>2</sup> hydrolyzes phospholipids including cephalin, sphingophospholipids and lysocephalin, destroys structural phospholipid and microvasculature, activates platelet activating factor and increases vascular permeability and ischemia<sup>[6]</sup>. The kallikren-kinin system produces bradykinin which dilates the blood vessel, increases vascular permeability and produces

hypotension, these are the earliest events occurring in acute pancreatitis. It had been found that injection of ascitic fluid containing high concentration of bradykinin to healthy animal produces hypotension<sup>[7]</sup>. But by giving bradykinin antagonist, HOE 140, the pancreatic edema caused by bradykinin can be reduced<sup>[8]</sup>. The above pancreatic enzymes not only induce autodigestion of pancreas, inflammation of peripancreatic fat, but also circulate in the blood together with the activated cytokines to the remote organs including the lung and brain causing damages. Besides, the release of pancreatic enzymes also activate complement system and thrombo-fibrinolytic system, producing thrombosis in the microvessels. In the ascitic fluid of severe acute pancreatitis patients, activated protease, phospholipase A<sub>2</sub>, bradykinin, complement component, histamine and some inflammatory mediators as platelet activating factor (PAF) and prostaglandin are found.

##### ***Release of cytokines***

During pancreatic necrosis and inflammation, IL-1 $\beta$ , IL-6, TNF- $\alpha$ -mRNA expression can be detected in the pancreas. The macrophages release IL-1, IL-6, TNF- $\alpha$  and IL-8, among which, IL-6 produces acute phase proteins, IL-8 chemotacts neutrophils to the inflamed areas, including the pancreas and the lung. The macrophages are the sources of proinflammatory cytokines (IL-1, IL-6, TNF- $\alpha$ ) and anti-inflammatory cytokines (IL-4, IL-10, IL-1ra), IL-1ra is IL-1 receptor antagonist, the IL-6 produced in severe acute pancreatitis is greater in amount than that produced in mild acute pancreatitis, and also persists longer<sup>[9]</sup>. These proinflammatory cytokines induce intercellular adhesive molecules (ICAM 1) and vascular adhesive molecules (VCAM) expression, promote the spread of inflammation, also augment the elastase of neutrophils to produce free radicals damaging the endothelial cells, causing endothelial swelling, and circulatory stasis<sup>[10]</sup>. In severe acute pancreatitis, increase of proinflammatory cytokines and decrease of anti-inflammatory cytokines are crucial factors in its progression, experimental study revealed that using TNF- $\alpha$  monoclonal antibody or recombinant IL-10, either of them could reduce the severity of the disease and increase the survival rates<sup>[11-14]</sup>.

PAF is the structural component of membrane lipid, it can be synthesized by endothelial cells, macrophages and platelets, and activated by PLA<sub>2</sub>, producing chemotaxis, aggregation, releasing superoxides, initiating the interaction of neutrophils and endothelial cells and favoring the entrance of neutrophils into the tissue space. It also causes increased vascular permeability of the capillary network of the lung, kidney, heart and the GI

tract<sup>[15]</sup>. Moreover, it enhances the tissue damage by the endotoxin liposaccharide, thus playing a crucial role in the pathogenesis of severe acute pancreatitis, it not only has autocrine and paracrine function, with high content it also has endocrine function, producing multiorgan dysfunction syndrome (MODS)<sup>[11]</sup>. In cerulein and taurocholic acid experimental models, its concentration is increased in the blood, ascitic fluid, pancreas, and lung tissue, producing pancreatic ischemia and increasing the inflammatory cellular infiltration. Recently it is claimed by using PAF antagonist, Lexipafant could decrease vascular permeability, diminish IL-6 and IL-8, and decrease the severity of ARDS, and turn the blood amylase and lipase to normal. In neutropenic patients or using neutrophilic cell antibody, the inflammation in the lungs could be attenuated<sup>[16]</sup>. 5-fluorouracil formerly used in the treatment of severe acute pancreatitis acted mainly via its upregulating effect of cytokine IL-4 and IL-10<sup>[17]</sup>.

#### ***Increased vascular permeability and Pancreatic microcirculatory impairment***

During early stage of acute pancreatitis, the arterioles in the pancreatic lobules constrict, with stasis of neutrophils in the postcapillary venules<sup>[18]</sup>, in addition, there is increased vascular permeability, these further decrease the pancreatic perfusion. Ischemia causes  $Ca^{2+}$  ion influx, aggravating rupture of lysosomal membrane and release of lysosomal enzymes. On the other hand, there is increase of  $TXB_2$  and  $TXB_2/PGI_2$  imbalance which constricts further the vessels and endothelin liberated by the damaged endothelium also decreases pancreatic blood flow. The release of  $TNF-\alpha$  also promotes vascular permeability, enhances platelet aggregation, stimulates excessive production of nitric oxide. The vessels in the region dilate, hence, the overall effect is the decrease of pancreatic vascular perfusion and blood stasis in the venular net work, leading to local intravascular coagulation. One can see fibrin deposition in the pancreatic capillaries under microscope, the interstitial pressure become elevated, the red blood cells migrate outward to extravascular space, contributing to the hemorrhage, ischemia, necrosis, inflammation and edema<sup>[18]</sup>. But the degree of edema is milder in the severe form. Not only is such in the pancreas substance, similar changes also occur in the pulmonary alveoli, the type II alveolar cells can be destroyed resulting in loss of pulmonary surfactant. Low molecular weight dextran and Dan Shen (*Salvia Miltiorrhiza*) liquid can improve the microcirculation and prevent pancreatic necrosis and lung changes<sup>[19]</sup>.

#### ***Infection-the second attack***

In severe acute pancreatitis patients, the cellular immunologic function is compromised, and the  $CD_4^+$  and  $CD_8^+$  lymphocytes are markedly diminished, but their ratio remains unchanged, which is quite different from that seen in mild acute pancreatitis<sup>[20]</sup>. Furthermore, because of increased vascular permeability due to PAF, there is loss of gastrointestinal epithelial barrier function<sup>[21]</sup>, the gut bacteria translocate from the colon to mesenteric lymph node, peritoneal cavity and blood circulation, IL-6 and IL-8 are further released by endotoxin,  $TNF-\alpha$  and IL-1 induction, IL-8 chemotacts and attracts more neutrophils accumulating at the pancreas, lung and other vital organs and tissues. Because of the insufficient endogenous superoxide dismutase, the deletion of glutathione, and presence of various oxygen free radicals destroy the cellular membrane, plasmalemma and the organelles<sup>[22]</sup>. Procoagulating factors are released leading to cascade of thrombo-fibrinolytic reaction, and produce inflammatory mediators from eicosanoid products. Moreover, the neutrophilic elastase is more destructive, causing multiorgan failure. Experimental studies showed that plasma neutrophilic elastase level paralleled the multiple organ failure in severe acute pancreatitis which were positively correlated. This is the so-called second attack theory<sup>[23]</sup>.

Serious complications of severe acute pancreatitis are mainly adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), infected necrosis and pancreatic encephalopathy, their pathogenesis are described as follows (Table 1).

Interstitial pulmonary edema and ARDS are caused by many factors: ① phospholipase  $A_2$  arrives at the lung by way of circulation, and destroys the type II alveolar cells, which are then unable to produce surfactant; ② the macrophages become vasuolated simultaneously, being unable to phagocytose and digest the protease and clear away the fibrin; ③ neutrophils being chemotacted and accumulated in the lungs, release the destructive elastase and oxygen free radicals; ④ PAF activated by  $PLA_2$  can damage the endothelium and increase the vascular permeability, causing ischemia, interstitial pulmonary edema and ARDS. If properly treated, this complication is now rarely seen.

DIC is often due to massive exudation in the peritoneal cavity and retroperitoneal space, hypoalbuminemia and hypovolemic shock, if colloid has not been instituted instantly, hypercoagulation might appear and followed by increased hematocrit, microcirculatory stasis and imbalance of thrombo-fibrinolysis. By given the author's treatment regime<sup>[24]</sup>, this complication has not been seen in recent years.

**Table 1 Complications of severe acute pancreatitis and their mechanisms**

Complications	Mechanisms
<b>1. Local complication</b>	
Intra and retro-peritoneal fluid collections	Bradykinin, TNF- $\alpha$ , PAF increase vascular permeability with fluid exudation Hypoalbuminemia
Pseudocyst	Unabsorbed fluid collection for long duration
Pancreatic fistula, transient	Pancreatic duct rupture, communicating with pseudocyst
<b>2. Systemic complications</b>	
Hypotension, hypovolemic shock	Increased vascular permeability, profuse exudation into peritoneal cavity Hypovolemia Hypoalbuminemia
Intestinal ileus, dehydration, hypokalemia	Peritonitis; loss of peristaltic function; large quantity of digestive fluid sequestered in intestinal lumen; infusion of large volume of crystalloid solution
Hypocalcemia	Formation of calcium soap plaques with fats on peritoneum and mesentery
Renal insufficiency	Hypotension, low blood volume, decrease of renal blood flow (PAF further decreases renal blood flow)
Gastric hemorrhage	Acute gastric mucosal bleeding
Jaundice	Pancreatic head edema in mild jaundice, choledocholithiasis in severe jaundice cases
Interstitial lung edema, ARDS	PLA <sub>2</sub> destroys structural phospholipid; PAF and TNF- $\alpha$ increase vascular permeability; Neutrophils release elastase and free radicals damage type I & II lung epithelial cells with disability of producing surfactants, alveolar atrophy and interstitial edema
Disseminated intravascular coagulation (DIC)	Shock, hypercoagulable state; microcirculatory stasis; imbalance of thrombo-fibrinolytic system; deletion of antithrombin III
Pancreatic encephalopathy	PLA <sub>2</sub> damages structural phospholipid of brain cell membrane; PAF increases intracerebral vascular permeability with brain edema and demyelination of grey and white matter
Transient blindness	Retinal ischemia; white cell emboli with exudation, increased vascular permeability
Infection, bacteremia, sepsis	Gut barrier dysfunction with translocation of gut bacteria and endotoxemia, bacteremia
Infected necrosis	Cellular immunity decreases, sepsis
Pancreatic abscess	Same as above, hemodynamic changes caused by inflammatory cytokines and inflammatory mediators
Heart failure	Underlying ischemic heart disease; overloading of circulation by massive infusion or too rapid intravenous dripping

Pancreatic encephalopathy is primarily due to the demyelination of the cerebral grey and white matter caused by PLA<sub>2</sub>, which can induce increased vascular permeability, the intravascular osmotic pressure decreases and the brain becomes more vulnerable to transudation, resulting in brain edema. With proper treatment, the recovery in patients aged below 40 is uneventful, those older than 60 especially those with previous history of cerebral infarction may have some sequela.

Infected necrosis and pancreatic abscess. The former usually occurs two weeks after the onset of the disease, the latter occurs four to five weeks after the onset. The invading bacteria usually derive from one's own GI tract, including the bacilli and cocci. The first five bacteria are *B. Coli*, *Klebsiella*, *Enterobacillus*, *Streptococcus faecalis* and other *Streptococci*, there can also be *Staphylococcus*, *Pseudomonas aeruginosa* or *Bacteroid fragilis*<sup>[25]</sup>. *E. coli* usually derives from

the colon, biliary tract, urinary tract or respiratory tract through hematogenous route, *Staphylococcus epidermis bacteremia* comes from venous catheterization or urinary catheterization. Pancreatic abscess rarely contains necrotic tissue, but frequently is composed of pure pus. If preventive measures are taken beforehand, sepsis and septicemia can be prevented and are now rarely seen.

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