The role of Kupffer cells in the progression of acute pancreatitis

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Abstract

Introduction
Acute pancreatitis is a kind of severe disease, its pathogenesis is not so clear. At present, more and more research shows that acute pancreatitis is also an inflammation disorder, which develops a complex cascade of immunological events. A large number of experiments show that activated macrophage (Kupffer cells, KC) can secrete a large quantity of cytokines, such as IL-1, IL-6 and tumour necrosis factor α (TNF-α), which enters the blood circulation and can increase the permeability of capillary, then facilitates the adhesion and exosmose of leukocytes, finally causing systemic inflammatory response syndrome (SIRS) and damage of organs. Blocking the function of KC improve the prognosis and mortality of acute pancreatitis would be decreased obviously. The aim of this review was to discuss the role of kupffer cells in the progression of acute pancreatitis.

Conclusion
KCs, as an important source of cytokines in AP, play a key role in acute pancreatitis-associated systemic damage. So far, the studies about the relationship between KCs and AP have all used animal models, but relationship KCs and AP in human beings remains unclear.

Introduction
Acute pancreatitis (AP) is one kind of severe diseases with a mortality of approximately 10%. As for severe acute pancreatitis, the mortality is more than 20%. The early pathophysiology of the disease is not well understood. It is widely accepted that the premature activation of digestive enzymes (trypsin, elastase and lipase) within the pancreatic acinar cells is a critical initiating event that leads to autodigestion of the pancreas

However, acute pancreatitis is also an inflammatory disorder, which develops a complex cascade of immunological events which not only affect the pathogenesis but also the course of the disease. Although inacin or interstitial activation of trypsinogen is most probably the trigger of acute pancreatitis, in recent years, much emphasis has been put on the role of leukocytes. In addition, a number of proinflammatory mediators have been identified to play a role in the progression of local pancreatic damage to systemic inflammation. This includes tumour necrosis factor α (TNF-α), inter-leukin (IL)-1β, IL-6, MCP-1 and Platelet activating factor. Some of these mediators are initially released by pancreatic acinar cells and results in the recruitment of neutrophils and monocytes.

Numerous experimental and clinical data indicate that more proinflammatory mediators including cytokines, arachidonic acid derivatives, activated oxygen species and proteases are released locally by over activated neutrophils and monocytes. KCs activation in AP causes more attention, so the purpose of this review is to discuss the role of KC in the acute pancreatitis-associated organ dysfunction.

Discussion
The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

KC activation in AP
Macrophages produce both pro and anti-inflammatory mediators, suggesting that these mediators play a key role in the progression of AP. Several reports demonstrate that mediators released in AP by the damaged pancreas could activate macrophages. In particular pancreatic enzymes such as trypsin, elastase, carboxypeptidase A and lipase induce the generation of TNF-α in cultured peritoneal macrophages or in macrophage cell lines. The fact that these effects are mediated by IKB degradation and nuclear factor-kb (NF-kb) activation indicates that these enzyme trigger macrophage activation through specific membrane-bound...
receptors789. Conversely, some researches show that TNF-α directly induces premature protease activation and necrosis in pancreatic acinar cells. This result suggests that targeting TNF-α for which pharmaceutical agents are readily available, it could be an effective treatment strategy that directly addresses the cellular causes of AP10.

In vitro activation of macrophages could also be observed by treating these cells with supernatants of pancreatic acinar cells cultures incubated with cerulein11. Similarly, ascitic fluid collected from rats after the induction of experimental models of AP activates macrophages in vitro12,13. As KCs are part of macrophages, it could be inferred that activation of KC in AP is similar to the activation of macrophages.

The molecular mechanism of KC in AP

Although the mechanism that how KCs produce cytokines is still not clear, some researchers have discovered that NF-kB plays an important role14. NF-kB is one kind of protein that can bind to the promoter or enhancer of some specific genes, starting the gene transcription and then controlling pro-inflammatory gene expression. In most cells, NF-kB is normally sequestered in the cytoplasm in an inactive form associated with a class of inhibitory proteins called IKBs. When AP occurs, NF-kB is rapidly activated and then translocates to the nucleus, binding to specific kB sequences in the promoter regions and starting downstream gene expression. Some studies have found that pancreatic peptidases can induce the activation of NF-kB and up-regulation of TNF-mRNA in KC. In this study, it was observed that when pyrolidine dithiocarbamate (PDTC, the NF-kB inhibitor) was added to the KC medium, production of TNF-α was inhibited, which showed that the activation of NF-kB was an essential part of cytokine production of KC15.

Jaffray et al. found that three specific pancreatic enzymes (elastase, carboxypeptidase A and lipase) induced TNF-α protein production from macrophages. This experiment demonstrated that elastase, carboxypeptidase A and lipase induced degradation of IKB-β (not IKB-α), activation of NF-kB and production of TNF-α, whereas inhibition of IKB with PDTC attenuated this response.

Macrophages can be induced by specific activated pancreatic enzymes and lipase TNF-α. This process is dependant on IKB-β degradation and NF-kB activation, suggesting that these enzymes trigger this second messenger system through specific membrane-bound receptors9. As KC is part of systemic macrophages, this experiment makes us understand the molecular mechanism of cytokine production of KC induced by trypsin.

This experiment also provides a reliable theoretical basis for the clinical treatment of inhibiting the enzyme. These findings have opened a window of opportunity for the use of selective NF-kB inhibitors in regulating the inflammatory process in AP.

KC and acute pancreatitis-associated lung injury

In patients with AP, up to 20% of all deaths occurring prior to admission to hospital. In these cases, acute lung injury (ALI) seems to be the predominant cause of death. Clinically, 50% to 75% of patients with severe acute pancreatitis (SAP) suffer pulmonary infection and about 20% of SAPs have ARDS.

The pathophysiological mechanism of ALI includes a variety of derangements of the normal homeostasis, including pulmonary endothelial and epithelial barrier dysfunction. In addition, neutrophils, monocytes and macrophages, being present both prior to challenge and recruited at different phases by cytokines like interleukin-8 (IL-8) and monocyte chemotactic protein (MCP-1), become activated, playing a central role in the progression of ALI.

KC can interact with mediators released by a damaged pancreas or present in acinar cells before they become diluted in the systemic circulation. Once the inflammatory mediators reach the liver, KCs become activated and amplify their release of cytokines into the bloodstream and thus contribute to the systemic manifestation of AP.

Activated KCs release e.g. immunoregulatory and inflammatory cytokines, reactive nitrogen intermediaters (RNI), reactive oxygen intermediaters (ROI) and hydrogen peroxide, all playing significant roles in the progression of pancreatic inflammation into a systemic process16,17.

Closa et al. performed an end-to-side portacaval shunt before acute hemorrhagic necrotizing pancreatitis (AHNP) induction in rats and found that during AHNP, portacaval shunting appears to exert a profound effect on ameliorating the inflammatory infiltrate. It is suggested that almost all the pancreatic enzymes and mediators released from the pancreas into the plasma during AHNP pass through the liver, indicating that this step is a determinant in the development of lung injury. These observations point to the key role of liver as a triggering mechanism for inflammatory process in the lung as a consequence of AHNP18,19.

Moreover, activation of hepatic inflammatory cells, especially KCs, plays a key role in the development of lung injury. Gloor and collaborators went on an experiment to confirm the liver's function during AP. The mice were divided to two groups— one group treated with gadolinium chloride (GdCl3), another without GdCl3, then they measured the level of cytokines in the portal vein was the lowest, while in the systemic circulation was the highest. In the treated group, the cytokine level in the portal vein and hepatic vein, and observed the degree of damage in the pancreas, liver and lung tissue. The results showed that in the untreated group, cytokine level in the portal vein was the lowest, while in the systemic circulation was the highest. In the treated group, the cytokine level in the hepatic vein and systemic circulation decreased, and damage contributed of lung tissue reduced significantly. This experiment showed that the liver effectively release measurable amounts of cytokines into the bloodstream in AP and also indicated KC derived cytokines had much to do with elevated levels of...
systemic cytokines and associated lung injury.20,21.

KCs and acute pancreatitis-associated liver injury

When AP occurs, it causes pancreatic acinar cells apoptosis and trypsin releasing, which further promote the release of a large number of inflammatory mediators. Once they go through the bloodstream to the liver, KCs are stimulated and activated, which causes a chain reaction and amplification by a series of biological reactions. Large numbers of cytokines are released, such as IL-2, IL-10, Fas/FasL etc. These cytokines are involved in the occurrence and development of SIRS.22 So far it has been thought that TNF-α is one of the most important cytokines involved in the pathophysiological mechanism. One study found that KC-mediated p38 mitogen-activated phosphokinase (p38 MAPK) activates NF-κB, which is related to the liver injury in SAP.23 Other studies have shown that TNF is a leading factor in inflammation in AP, which enables hepatocyte apoptosis and necrosis and finally leads to severe liver damage.24

Some researchers have demonstrated that KC-derived FasL mediates liver injury in AP and sought to determine its role in AP-induced hepatocyte apoptosis. Gallagher’s study showed that AP induced apoptosis by transcriptional activation of Fas/FasL. AP-induced apoptosis was significantly reduced in Fas/FasL knockout mice.25 Yang et al. have found that pancreatic elastase up-regulates FasL within KCs. FasL induces hepatocyte injury and death and up-regulates p38 MAPK within hepatocytes.26

Wei’s study suggested that taurine pre-treatment ameliorated liver injury in rats with SAP, mainly by inhibiting phosphorylated p38 MAPK and NF-κB activating in KCs, which may play an important role in liver injury.27 Peng et al. showed that the deletion of Toll-like receptor-4 (TLR4) attenuated liver injury in AP. This study also found that besides the augmentation of TLR4 mRNA in mice liver, an increment in protein kinase C-zeta (PKC-zeta) was detected. PKC-zeta induces nuclear translocation of NF-κB, which plays a key role in cytokine production of KC in AP. Deletion of TLR4 down-regulates PKC-zeta, NF-κB and attenuates pancreatitis-induced hepatocyte apoptosis and then alleviates liver damage in AP.28

KCs and acute pancreatitis-associated systemic infection

It is known that during AP, the intestinal permeability increases and function of intestinal mucosal barrier decreases, leading to intestinal bacterial translocation and the endotoxin going into the blood circulation. It causes bacterial infection and endotoxemia, leading to SIRS and multiple organ dysfunction (MODS), which are responsible for the death of patients with AP. Stenback et al.29 have found that when KC function is completely blocked, intestinal bacterial translocates to the liver, spleen, and lung, which suggests that KCs play a role of a barrier in the prevention of bacterial translocation and it indicates that KCs functioning properly prevents the systemic infection caused by bacterial translocation.

Conclusion

KCs, as an important source of cytokines in AP, play a key role in acute pancreatitis-associated systemic damage. So far, the studies about the relationship between KCs and AP have all used animal models, but relationship KCs and AP in human beings remains unclear. Therefore we need to carry on more studies in other models. Studies should be done to discuss the relationship between KCs and other organ dysfunction. We believe that further studies of KCs will help to establish more effective novel therapies for AP management.

References