Role of platelet-activating factor in pathogenesis of acute pancreatitis

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Abstract

Platelet-activating factor (PAF) is a potent proinflammatory phospholipid mediator that belongs to a family of biologically active, structurally related alkyl phosphoglycerides with diverse pathological and physiological effects. This bioactive phospholipid mediates processes as diverse as wound healing, physiological inflammation, angiogenesis, apoptosis, reproduction and long-term potentiation. PAF acts by binding to a specific G protein-coupled receptor to activate multiple intracellular signaling pathways. Since most cells both synthesize and release PAF and express PAF receptors, PAF has potent biological actions in a broad range of cell types and tissues. Inappropriate activation of this signaling pathway is associated with many diseases in which inflammation is thought to be one of the underlying features. Acute pancreatitis (AP) is a common inflammatory disease. The onset of AP is pancreatic autodigestion mediated by abnormal activation of pancreatic enzyme caused by multiple agents, which subsequently induce pancreatic and systemic inflammatory reactions. A number of experimental pancreatitis and clinical trials indicate that PAF does play a critical role in the pathogenesis of AP. Administration of PAF receptor antagonist can significantly reduce local and systemic events that occur in AP. This review focuses on the aspects that are more relevant to the pathogenesis of AP.

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Key words: Platelet-activating factor; Signal transduction; Pancreatitis; Pathogenesis

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INTRODUCTION

Inflammatory reaction is a common pathophysiological process. Appropriate inflammatory reaction has protective effects, but excessive reaction often induces injury. The underlying pathological changes of inflammation include exudation, alteration, and proliferation, which are the outcomes mediated by inflammatory mediators such as platelet-activating factor (PAF), leukotriene, tumor necrosis factor alpha (TNF-α), and interleukin-1 (IL-1). Numerous researches have shown that PAF is one of the most potent mediators in many inflammatory processes, and not only induces inflammatory reaction but also mediates synthesis and release of other mediators to aggravate the degree of inflammation.

Acute pancreatitis (AP) is a common clinical inflammatory disease. A single injection of PAF into the superior pancreaticoduodenal artery of rabbits induces dose-dependent morphologic alterations of pancreatic tissue and increases serum amylase levels[1]. Murine pancreatic acini synthesizes PAF[2] and pancreatic vascular endothelium expresses PAF receptor[3]. These findings suggest that this mediator may have a role in AP. AP is usually classified into mild and severe type. Severe acute pancreatitis (SAP) still has a high mortality rate, while the pathogenesis of AP is not well-defined. There is growing evidence that pathogenetic factors deciding the severity of AP are complicated. PAF has been strongly implicated in the development of AP.

Here we have reviewed the role of PAFs such as excessive leukocyte stimulation, microcirculatory disorder, gut endothelial barrier dysfunction, bacterial translocation, acinar cell necrosis and apoptosis in the pathogenesis of AP.

BIOLOGICAL CHARACTERISTICS OF PAF

Phospholipids are the major components of cellular membrane and are also known to be the source of arachidonic acid, which is metabolized into bioactive eicosanoids. Some phospholipids, including lysophosphatidic acid, sphingosine-1-phosphate, and PAF, exert bioactive effects. The term PAF is used because it
was first described as the substance responsible for the aggregation of platelets released from rabbit basophils after IgE stimulation. Although PAF is still commonly used, it has diverse and potent physiological effects. The chemical structure of PAF is 1-O-alkyl-2-acyl-sn-glycero-3-phosphocholine determined in 1979 by three independent laboratories.

Two distinct pathways for the synthesis of PAF have been demonstrated: the remodeling pathway and de novo pathway. The remodeling pathway is mainly involved in the synthesis of PAF by stimulated inflammatory cells. The activities of lyso-PAF acetyltransferase (lyso-PAF AcT) and PAF-synthesizing phospholipase transferase (PAF-PCT) are directly responsible for PAF synthesis. Lyso-PAF AcT catalyzes the transfer of acetyl moiety from acetyl CoA to free hydroxyl at sn-2 position of 1-alkyl-sn-glycero-3-phosphorylcholine. PAF-PCT catalyzes the conversion of 1-alkyl-2-acyl-sn-glycero-3-phosphocholines to PAF. The synthesis and catabolism of PAF are highly regulated. The final molecular composition of PAF in tissues and the expression of its biological activities depend on the activation of catabolic pathways. The most important enzyme in limiting the PAF bioactivity is a PAF-specific acetylhidrolase (PAF-AH), which cleaves the short acyl chain at sn-2 position and forms biologically inactive lyso-PAF.

A diverse array of cells has been shown to synthesize PAF upon appropriate stimulation. In particular, PAF is produced by a variety of cells such as monocytes/macrophages, polymorphonuclear leukocytes (PMN), eosinophils, basophils, platelets, mast cells, vascular endothelial cells, and lymphocytes, which may participate in the inflammatory reaction. Murine pancreatic acini can also synthesize PAF induced by cerulein. PAF is a phospholipid mediator possessing a wide spectrum of potent proinflammatory action. In vitro, PAF promotes chemotaxis, aggregation, granule secretion, and oxygen radical generation of leukocytes and adherence of leukocytes to the endothelium. Moreover, PAF is involved in allergy, wound healing, atherosclerosis, angiogenesis, and PAF possess PAF receptors and are targets for PAF action. The pancreatic vascular endothelium also expresses PAF receptor. It has been demonstrated that PAF binds to the receptor and activates the associated G protein. In turn, G protein activates a phospholipid-specific PLC which hydrolyzes a membrane phospholipid, phosphatidylinositol 4, 5-bisphosphate (PIP2), to generate two second messengers: diacylglycerol and inositol 1,4,5-trisphosphate (IP3). These compounds mediate the release of Ca2+ from intracellular store (ER) and activation of protein kinase C (PKC), respectively. Moreover, it has been shown that PAF can activate mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun N-terminal kinase (JNK). Using human umbilical vein endothelial cells (HUVECs) as a model system, Deo et al. suggested for the first time that PAF activates perussis toxin-insensitive Gαz protein upon binding to its seven transmembrane receptors and adenylate cyclase, as well as elevates cAMP levels, which activate protein kinase A (PKA). PAF exposure induces the expression of TIMP2 and MT1-MMP and binding of p130Cas, Src, SHC, and paxillin to FAK. It was found that PAF is capable of stimulating nuclear factor kappa B (NF-xB) activation and transcription of c-fos and c-jun genes in inflammatory cells.

INVoLVErnENT OF PAF IN THE PATHOGENESIS OF AP

AP is a common clinical condition and is usually classified into mild and severe type. SAP is characterized by acute morbidity, rapid progression, multiple complications, and high mortality rate. While the pathogenesis of AP is not well-defined, considerable advances have been made in this research field. At present, it is considered that severity of pancreatitis is associated with excessive leukocyte stimulation, microcirculatory disorder, gut endothelial barrier dysfunction, bacterial translocation, and acinar cell necrosis and apoptosis. In the pathogenesis of AP, PAF has been strongly implicated (Table 1).

Role of PAF in excessive leukocyte stimulation

In the course of AP, abnormal intra-acinar cell activation of digestive enzymes induced by diverse stimuli triggers morphopathological changes in pancreatic and adjacent tissues, such as inflammation, edema, hemorrhage, necrosis, and even systemic manifestations. In 1988, Rinderknecht proposed the hypothesis of excessive leukocyte stimulation. Consequently, a great number of studies have demonstrated that the initial injury results in the expression of inflammatory mediators such as PAF.
Role of PAF in microcirculatory disorders

A number of experimental studies suggest that pathogenesis of AP correlates with microcirculatory disorders. Many complications of SAP are due to the amplifying effects of microcirculatory disruption. Constriction of interlobular pancreatic arteries 2 min after intraductal infusion of sodium taurocholate has been observed, indicating that microcirculatory changes may occur in early AP. There is evidence that pancreatic microcirculatory changes are closely related to the process of AP. Ligating duodenum over half its circumference at 2 cm on either side of the duodenal entry of the biliopancreatic duct induces histopathologic alterations of the pancreas such as edema, parenchymal necrosis, thrombosis and hemorrhage, indicating that tissue ischemia plays a role in increasing the severity of pancreatitis.

Many vasoactive mediators activated during the inflammatory response to pancreatic injury can cause microcirculatory disorders in AP. PAF is one of the most important mediator. Increased microvessel permeability caused by PAF may be related to direct endothelial cell activation, adhesion molecule expression, and leukocyte activation. Synthesis of PAF by endothelial cells at the site of plasmin generation may render the endothelial cell surface pro-adhesive for neutrophils and favor a local increase in vascular permeability. Recent data suggest that PAF is able to directly modulate microvascular permeability and increase venular permeability. Increased capillary permeability permits sequestration of macromolecules and fluid, which causes a deficiency of circulating blood volume and microcirculatory disorders. Predominant microcirculatory disorders are nutritive capillary perfusion failure, with the consequence of prolonged focal hypoxia or anoxia, and inflammation-associated microvascular leukocyte recruitment, CD11b and intercellular adhesion molecule (ICAM)-1-mediated leukocyte-endothelial cell interaction and loss of endothelial integrity, which may result in both edema formation and necrosis. Moreover, vasospasm and microthrombi formation due to hypercoagulability can also lead to the deterioration of pancreatic microcirculation and pancreatic necrosis.

It has been shown that the treatment of AP with PAF antagonists can significantly improve capillary blood flow in the pancreas and colon, renal, and respiratory function as well as survival rate, stabilize capillary permeability, decrease fluid loss into the third space. The partial protective effect of PAF antagonists further supports the role of PAF in microcirculatory disorders.

Role of PAF in gut endothelial barrier dysfunction

Gut endothelial barrier dysfunction is a critical factor for the development of tissue injury and organ dysfunction in AP. The study on dogs colonized with a strain of *Escherichia coli* (*E. coli* 6938K) bearing plasmid pUC4K showed that most dogs with severe pancreatitis have ischemic changes in the small bowel mucosa and *E. coli* translocation to the pancreas and mesenteric lymph nodes (MLNs), suggesting that the gut is a primary source of infection in pancreatitis.
Pancreatitis is characterized by very little necrosis but a high degree of apoptosis, suggesting that apoptosis may be a teleologically beneficial response to acinar cell injury in general, especially in AP. Deficiency of pancreatic connexin converts reversible AP into severe disease and decreases the sensitivity of acinar cells to apoptotic stimuli, demonstrating that apoptosis determines the severity of AP.

It has been reported that PAF is involved in acinar cell damage. Treatment with antineutrophil serum (ANS) and BN52021 can prevent inflammatory responses caused by cerulein and decreases cell damage. Treatment with ANS increases apoptosis in cerulein-infused animals, indicating that cerulein stimulates pancreatic production of PAF. PAF mediates both apoptosis and neutrophil chemotaxis in the pancreas. Neutrophils in turn may convert acinar cells undergoing apoptosis to necrotic cells.

**THERAPEUTIC EFFECTS OF PAF ANTAGONISTS ON AP**

Recent studies have established the critical role of inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, IL-10, PAF, C5a, ICAM-1 and substance P, in the progression of AP from local pancreatic inflammation to a systemic inflammatory disease. Elucidation of the key mediators in AP coupled with the discovery of specific inhibitors makes it possible to develop clinically effective anti-inflammatory therapy. At present, a number of inflammatory mediator antagonists are tested. PAF antagonists, including ginkgolide B (BN52021), lexipafant (BB-882), CV-6209, TCV309, and WEB-2170, etc., have shown beneficial effects on the manifestations of AP. In experimental pancreatitis and clinical trials, administration of several PAF antagonists significantly reduces the level of serum amylase, leukocyte infiltration, and improves capillary blood flow in the pancreas and distant organs, renal and respiratory function, and survival rate.

In animal pancreatitis model, ginkgolide B could significantly reduce vascular permeability, pancreatic edema, hyperamylasemia, diminute superoxide dismutase (SOD) activity, and inhibit lipid peroxidation in pancreatic tissue. These changes are accompanied with significant reduction of acinar cell vacuolization and remarkable inhibition of inflammatory cell infiltration in the interacinar space.

In addition, treatment with ginkgolide B has shown protective effects on slow mesenterio-angial small arteriolar and venular blood flow velocity and dilated mesenterio-angial small venular diameter at the early phase of AP. Moreover, ginkgolide B reduces bacterial translocation to distant sites, has a significant effect on serum pancreatic enzymes and histologic score of pancreatitis, and suppresses elevation in IL-6 levels. Preventing bacterial dissemination in early AP may have beneficial effects on the evolution of this disease. Furthermore, ginkgolide B decreases malondialdehyde accumulation in pancreatic tissue, prevents sulphydryl depletion in lung tissue, necrotic and inflammatory changes in the pancreatic tissue, and improves survival rate. Activation of pulmonary alveolar macrophages (PAMs) might play an important role in...
severe complications of AP. Ginkgolide B reduces total and free activity of lysosomal hydrolases of PAMs and partly prevents labilization of their lysosomal membranes. Therefore, an important mechanism of ginkgolide B underlying pulmonary complications of AP is to stabilize PAM lysosome.\(^{46}\) Moreover, BN50739 can reduce intestinal injury, levels of endotoxin and bacterial counts in the portal blood, MLNs and pancreas and increase intestinal mucosal blood flow.\(^{117}\) In pigs with SAP, pre- and post-treatment with BN50739 can effectively reduce PAF levels in lung and tracheal mucosa and the severity of acute lung injury following SAP by reducing PMN sequestration and the amount of elasate, or by inhibiting PLA\(_2\) activities in lung and tracheal mucosa.\(^{118}\)

In rats with AP induced by intraductal infusion of 5 g/L sodium taurodeoxycholate, pretreatment with lepxafant could reduce pancreatic endothelial barrier dysfunction and severity of pancreatitis-associated intestinal dysfunction as well as systemic concentrations of IL-1 and local le Felixxuate recruitmente\(^{55,56}\). AP lepxafant reduces the activity of serum cytokines (TNF-α, IL-1β), lung myeloperoxidase (MPO) and serum amylase.\(^{68}\) Lepxafant treatment can decrease bacterial spread to distant sites in AP induced by pressure injection of 3% taurocholate and trypsin into the common biliopancreatic duct.\(^{69}\)

In rats, TCV-309 administered prior to cerulein and/or PAF reduces cerulein-induced pancreatitis and prevents PAF-induced pancreatitis.\(^{50}\) It was reported that treatment with TCV-309 before septic challenge effectively prevents hyperactivity of bronchoalveolar macrophages and pancreatitis-associated lung injury by reducing serum concentrations of cytokine-induced neutrophil chemoattractant (CINC) and CINC messenger RNA (mRNA) in the lung, as well as pulmonary infiltrates immunoreactive for CINC or Mac-1 (CD11b/CD18).\(^{71}\)

CONCLUSION

In the pathogenesis of AP, PAF exhibits pleiotropic function and is involved in both local pancreatic injury and systemic multiple organ damage. The effectiveness of PAF antagonists depends not only on their ability to block the effects of inflammatory mediators but also on their administration early enough in the course of pancreatitis before pancreatic necrosis or organ dysfunction occur. PAF antagonist therapy for systemic inflammatory response syndrome and multi-organ dysfunction syndrome in the management of patients with SAP has been considered as an important advance in the treatment of these patients.

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