Role of phosphoinositide 3-kinase in the pathogenesis of acute pancreatitis

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Abstract

A large body of experimental and clinical data supports the notion that inflammation in acute pancreatitis has a crucial role in the pathogenesis of local and systemic damage and is a major determinant of clinical severity. Thus, research has recently focused on molecules that can regulate the inflammatory processes, such as phosphoinositide 3-kinases (PI3Ks), a family of lipid and protein kinases involved in intracellular signal transduction. Studies using genetic ablation or pharmacologic inhibitors of different PI3K isoforms, in particular the class I PI3Kα and PI3Kγ, have contributed to a greater understanding of the roles of these kinases in the modulation of inflammatory and immune responses. Recent data suggest that PI3Ks are also involved in the pathogenesis of acute pancreatitis. Activation of the PI3K signaling pathway, and in particular of the class IB PI3Kγ isoform, has a significant role in those events which are necessary for the initiation of acute pancreatic injury, namely calcium signaling alteration, trypsinogen activation, and nuclear factor-κB transcription. Moreover, PI3Kγ is instrumental in modulating acinar cell apoptosis, and regulating local neutrophil infiltration and systemic inflammatory responses during experimental acute pancreatitis. The availability of PI3K inhibitors selective for specific isoforms may therefore provide new therapies to improve the clinical course of this disease. This article presents a brief summary of PI3K structure and function, and highlights recent advances that implicate PI3Ks in the pathogenesis of acute pancreatitis.
INTRODUCTION

The process of pathologic autodigestion, triggered by prematurely activated digestive enzymes produced by acinar cells, has long been indicated as the key event for the initiation of acute pancreatic injury. Recent research efforts have begun to clarify the biochemical mechanisms inducing intracellular zymogen activation, which include pathologic calcium signaling, alterations of intracellular trafficking that lead to the colocalization of lysosomal and zymogen-containing vacuoles, early activation of the nuclear factor-kappa B (NF-κB) pathway, autophagy, and oxidative stress. Intracellular zymogen activation results in acinar cell necrosis and local inflammatory responses, which progressively resolve in most patients. However, sustained inflammation may lead to the development of local and systemic complications and/or organ dysfunctions, which occur in about 20% of all cases of acute pancreatitis and account for the high mortality (10%-30%) of patients affected by severe acute pancreatitis.

A large body of experimental and clinical data supports the notion that inflammation in acute pancreatitis has a crucial role in the pathogenesis of local and systemic damage and represents a major determinant of clinical severity. Increased levels of circulating inflammatory cytokines, chemokines and other humoral mediators have been reported in patients with acute pancreatitis, as well as in experimental in vivo and ex vivo (hyperstimulated acinar cells) models of the disease condition.

The molecular process underlying this event involves activation of specific transcription factors in the pancreatic tissue, including NF-κB, which is the most studied and best characterized of the transcription factors involved. These humoral mediators, in turn, recruit neutrophils and then other immune cells from the bloodstream, such as macrophages, monocytes and lymphocytes, which amplify and sustain the inflammatory reaction in the pancreatic tissue. Furthermore, experimental anti-inflammatory approaches - ranging from genetic deletion of cytokine receptors or specific integrins, neutralization of cytokines, chemokines, adhesion molecules or other mediators, blockade of neutrophil recruitment, or complement inhibition - have resulted in a significant reduction of mortality. However, whereas these experimental studies greatly improved our knowledge on the role of inflammation in the pathogenesis of acute pancreatitis, their results have not led to a progression in the treatment of patients affected by acute pancreatitis, and the few clinical trials conducted to date have yielded poor results. Therefore, it is not surprising that research concerning the pathogenesis of acute pancreatitis has recently focused on the role of phosphoinositide 3-kinases (PI3Ks), a family of lipid and protein kinases involved in intracellular signal transduction and modulation of inflammatory and immune responses. This article presents a brief summary of PI3K structure and function, with particular attention paid to their role in inflammatory pathologies, and discusses the recent advances involving PI3Ks in the pathogenesis of acute pancreatitis.

CLASSIFICATION AND STRUCTURE OF PI3KS

PI3Ks are a class of enzymes involved in intracellular signal transduction that were first described in the late 1980s. They possess both protein and lipid kinase activity, with the latter function being the most extensively studied. PI3Ks have historically been divided into three classes based on protein structure and substrate specificity.

Class I PI3Ks rely on the functional association of a catalytic subunit and a regulatory subunit, the latter of which modulates the activity of the heterodimer as well as its targeting to the plasma membrane upon receptor ligation, thereby allowing the enzyme access to the phosphatidylinositol substrates. Class I PI3Ks have been further divided in two subgroups: IA and IB. Class IA includes three members, PI3Kα, PI3Kβ and PI3Kδ, which are heterodimers composed by a specific p110 catalytic subunit (p110α, p110β and p110δ) and a regulatory p85 subunit. These isoforms are activated following stimulation of tyrosine kinase receptors, which include many growth factor receptors, such as those for epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, growth hormone, insulin-like growth factor, insulin and many interleukins (ILs). Nonetheless, a certain degree of isoform specificity has been demonstrated for several biological processes. For example, activation of the tyrosine kinase insulin receptor largely depends exclusively on PI3Kα. On the contrary, PI3Kδ is specifically recruited in immune cells upon the activation of T and B cell receptors, natural killer stimulatory receptors, Fc receptors, and Toll-like receptors. In addition, although class I PI3Ks usually act downstream of receptor tyrosine kinases, PI3Kβ is more effectively activated by G-protein-coupled receptors (GPCRs) than by tyrosine kinases. PI3Kγ is the only member of the PI3K class IB, and its structural organization is represented by the association of either a p84/p87 or p101 regulatory subunit with the p110γ catalytic subunit. PI3Kγ is activated by direct binding with G-protein βγ subunits, thus signaling downstream of GPCRs, such as chemokine receptors. Moreover, PI3Kγ signaling activity can further be potentiated by Ras-GTP. The main class I PI3K activity relies on the phosphorylation of phosphoinositides at the D3 position of the inositol ring, which leads to conversion of phosphatidylinositol (4,5)-bisphosphate to the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3, upon membrane translocation, binds...
with high affinity to the pleckstrin homology (PH) domain of its many effectors. These effectors include protein kinases Akt/ protein kinase B (PKB), PDK1, Btk, GAP, and GEF for small GTPases, which mediate fundamental intracellular signaling events implicated in cell proliferation and migration, metabolic homeostasis, and cell survival. The signaling activity of class I PI3Ks is finely regulated by at least two lipid phosphatases, namely the SH2-containing inositol phosphatases 1 and 2 and the phosphatase and tensin homolog, which respectively dephosphorylate the inositol ring of PIP3 on position 5 or 4. 

The tissue distribution of class I PI3K isoforms is quite different: PI3Kδ and PI3Kβ are widely expressed, whereas PI3Kγ and PI3Kδ are mainly expressed in leukocytes. However, the expression of PI3Kγ has also been reported in the heart and in the endothelium, as well as in breast and pancreatic cancers. Analogously, PI3Kδ expression has also been demonstrated in neurons, and in melanoma and breast cancer cells. Class II PI3Ks are high molecular mass monomers, characteristically containing C2 and Phox homology (PX) domains that are fundamental for localization at the plasma membrane. Their specific mechanism of activation and signaling, as well as their physiologic role in the regulation of cellular functions or their involvement in the pathogenesis of human diseases have only recently begun to be elucidated by the research. For example, class II PI3K-C2α has been demonstrated as critically required for endocytosis and for vascular integrity. Interestingly, PI3K-C2γ is expressed in the exocrine pancreas, but its role in this organ remains largely unknown.

Finally, class III PI3K includes only one member, vascular protein sorting 34 (VSP34), which is only able to generate phosphatidylinositol 3-phosphate. The physiologic importance of VSP34 and/or its involvement in human pathology are currently unclear.

Although very little is known about class II and III PI3Ks, there is increasing interest in developing inhibitors of these two classes for use as anticancer agents.

**ROLE OF PI3KS IN INFLAMMATORY CELLULAR RESPONSES**

The involvement of PI3Ks in inflammation has been recently highlighted by studies using genetic or pharmacologic inhibition of different PI3K isoforms. Genetic ablation of PI3Kα and PI3Kβ was lethal during embryonic development, however, PI3Kγ and PI3Kδ knock-out mice were viable and mainly showed alterations of both innate and adaptive immune responses. Ultimately, these results led to a better characterization of the regulatory role of these two PI3K isoforms in inflammatory pathologies.

PI3Kγ and PI3Kδ act in partnership to regulate the recruitment of neutrophils and monocyte/macrophages to the site of inflammation and then to coordinate the respiratory burst. PI3Kγ-null mice, neutrophils and macrophages display reduced migration in response to different stimuli that act through GPCRs, such as N-formylated peptides (fMLPs), C5a, or IL-8. In addition, in vivo investigation of a peritonitis mouse model showed highly impaired leukocyte recruitment. On the contrary, PI3Kδ appears to be specifically involved in regulating the directional neutrophil movement in response to chemotactic agents. Endothelial activity of both PI3Kγ and PI3Kδ also has a role in regulating neutrophil adhesion to inflamed vessel wall. At the inflammatory sites, PI3Kγ and PI3Kδ also cooperate in order to regulate the production of reactive oxygen species; this is a biphasic process in which the initial phase is dependent on PI3Kγ activation and is followed by an amplification phase mediated by PI3Kδ.

In addition to the roles of PI3Ks in neutrophils and monocytes, these kinases also regulate fundamental cellular functions in mast cells and eosinophils. Pharmacological inhibition of PI3Kδ reduces degranulation and cytokine release induced in mast cells by immunoglobulin (IgE) stimulation and protects mice from passive cutaneous anaphylaxis induced by IgE and antigen injection. In addition, inhibition of PI3Kγ decreases adenosine-induced mast cell degranulation and resistance to passive systemic anaphylaxis, demonstrating a specific role for this kinase in sustaining and maximizing mast cell degranulation. Furthermore, PI3Kγ is involved in eosinophil recruitment, modulation of allergen-induced eosinophilic airway inflammation, and airway remodeling.

PI3Kγ activity is also involved in regulation of the cellular functions of T and B lymphocytes, the main actors of the adaptive immune response. Both PI3Kγ and PI3Kδ are considered crucial for T cell development and function, since knock-out mice for either one or the other kinase show reduced numbers of peripheral T lymphocytes and increased ratios of double-negative (CD4 CD8) to double positive (CD4 CD8) cells in the thymus. Moreover, PI3Kδ is heavily involved in CD4+ T cell maturation and differentiation in distinct T cell subsets, whereas PI3Kγ is involved in T cell receptor-stimulated proliferation and cytokine production. PI3Kδ is also involved in the regulation of B cell maturation and activation. PI3Kδ-null mice showed an increased proB/preB ratio, which was due to a blockade of the maturation process that occurs between these two stages, as well as reduced IgM and IgG antibody responses, which were associated with a paradoxical increase in production of IgE. In line with these critical functions, PI3Kδ and PI3Kγ/δ inhibitors show important anti-proliferative activity in different forms of human hematologic malignancies, with particular efficacy in lymphomas.

**PI3KS IN INFLAMMATORY DISEASES**

PI3Kγ and PI3Kδ have been extensively investigated as
potential therapeutic targets in autoimmune and allergic diseases, and in pathologic conditions where inflammation has a crucial role for onset and progression\[44-46\].

Blockade of PI3Kδ by genetic ablation or by using selective pharmacological inhibitors reduces the incidence and severity of disease in the MRL-1pr mouse model of systemic lupus erythematosus\[108\] and in two different experimental models of rheumatoid arthritis, induced either by collagen injection or by transgenic overexpression of human tumor necrosis factor-α\[106,107\]. Inhibition of PI3Kδ also reduces inflammation and bone and cartilage erosion in a model of arthritis induced by the administration of arthritogenic serum\[109\].

Consistent with the role of PI3Ks in mast cell and eosinophil activation\[93-97\], genetic ablation of PI3Kδ reduces leukocyte infiltration, hyper-responsiveness, and airway remodeling in an ovalbumin (OVA)-induced model of asthma\[98\]. Similarly, inhibition of PI3Kδ either by genetic ablation or specific inhibitors decreases eosinophil infiltration, T helper cell (Th2) cytokine production (IL-4, IL-5 and IL-13), bronchial inflammation, and airway remodeling in the same OVA-induced asthma model\[110,111\].

PI3Ks are also involved in the pathogenesis of cardiovascular diseases in which inflammation has a relevant role, namely atherosclerosis and myocardial infarction\[46\]. PI3Kδ inhibition is effective in reducing plaque size in a model of early-stage atherosclerosis (apolipoprotein E-null mice)\[112\] and in the more aggressive low-density lipoprotein receptor knockout (LDLR\(−/−\)) model that mimics progressive familial hypercholesterolemia\[113\]. Interestingly, transplantation of bone marrow from PI3Kδ-null mice into LDLR\(−/−\) mice also reduces plaque size\[113\], indicating that the formation of atherosclerotic lesions is regulated by PI3Kδ expressed by immune cells. Moreover, PI3Kδ inhibition has been found to influence cellular composition of atherosclerotic plaques (as suggested by the observation of a reduction of infiltrating macrophages and T cells) and to increase plaque stability\[113\]. Finally, in agreement with the pathogenic role of inflammation in ischemia-reperfusion injury, TG100-115, a dual inhibitor of PI3Kδ and PI3Kδ, reduces infarct size and preserves myocardial function in an in vivo model of myocardial infarction\[114\].

**PI3KS IN ACUTE PANCREATITIS**

Little is known about the physiological role of PI3Ks in pancreatic acinar cells\[115,116\]. However, pharmacologic analysis has implicated PI3Kδ in cholecystokinin (CCK)-induced phosphorylation of p70S6 kinase and focal adhesion kinase and in regulation of exocytosis\[117\].

The involvement of PI3Ks in the pathogenesis of acute pancreatitis was first demonstrated in a study by Singh et al\[119\] using two unrelated inhibitors of all PI3K isoforms, wortmannin and LY294002, in two different rodent models of acute pancreatitis, one induced by supramaximal secretagogue stimulation and the other by duct injection. In the cerulein-induced model, wortmannin administration inhibited early trypsinogen activation, an effect associated with reduced redistribution of cathepsin B and intracellular colocalization of lysosomal hydrolases with digestive enzyme zymogens\[119\]. Moreover, wortmannin reduced the extent of pancreatic edema, neutrophil sequestration within the pancreas, acinar cell necrosis, and hyperamylasemia in the same model. Wortmannin also reduced pancreatic trypsin activity, acinar cell necrosis and myeloperoxidase activity in the second acute pancreatitis model, which had been induced by retrograde infusion of the rat pancreatic duct with the bile salt sodium taurocholate. In vivo experiments showed that wortmannin and LY294002 inhibited cerulein-induced trypsinogen activation without affecting the changes to the cytoskeleton of acinar cells that had been induced by supramaximal cerulein stimulation, in particular the redistribution of F-actin from subapical to basolateral areas\[118\]. The authors also performed experiments aimed to identify which class of PI3K was involved in trypsinogen activation during pancreatitis, initially directed toward class I PI3K because of its known association with GPCRs, such as CCK receptors. However, supramaximal concentrations of cerulein, those that induced ex vivo trypsinogen activation, did not increase phosphatidylinositol-3,4-bisphosphate nor PIP\(_2\), nor did they induce phosphorylation of Akt/PKB in ex vivo experiments\[119\], suggesting that class I PI3K were not involved. These results differ from those previously reported by another group, which had shown formation of class I PI3K products after stimulation with maximal concentrations of cerulein\[108\]. On the contrary, both in unstimulated and cerulein-stimulated acini, wortmannin decreased levels of the product of class III PI3K, phosphatidylinositol 3-phosphate, which is implicated in vesicle trafficking and fusion\[119\]. The authors proposed that cerulein-induced intra-cellular trypsinogen activation may be a consequence of perturbed vesicle trafficking induced by the accumulation of the phosphatidylinositol 3-phosphate class III PI3K product in a yet unidentified subcellular compartment\[119\].

Subsequent studies by different research groups have further analyzed the specific role of the PI3Kδ isoform in the pathogenesis of acute pancreatitis. Gukovsky et al\[120\] used PI3Kδ-deficient mice as well as pharmacologic PI3K inhibitors to investigate the role of PI3K in CCK-induced responses in isolated pancreatic acinar cells. These experiments showed that both PI3Kδ genetic ablation and PI3Kδ inhibition greatly diminished the CCK-induced calcium response in pancreatic acini by inhibiting both intracellular calcium mobilization and calcium influx, showing that PI3Kδ is required for pathologic calcium responses to CCK hyperstimulation\[120\]. Further studies by the same group demonstrated that PI3Kδ regulates calcium signaling in pancreatic acinar cells by inhibiting sarcoplasmic reticulum calcium-ATPase\[121\]. In addition to its regulatory role on calcium signaling, PI3Kδ is also implicated in regulating trypsinogen activation\[121\]. CCK-induced trypsinogen activation was, indeed, reduced
by about 60% in pancreatic acini isolated from PI3Kγ-null mice[124], an effect that may also be partially mediated through calcium signaling[125,126]. Finally, both PI3K inhibitors and PI3Kγ genetic deletion inhibited CCK-induced NF-κB activation in viva, indicating a regulatory role for PI3Kγ in the NF-κB response[127]. This result did not confirm those previously reported by Singh et al.[119] in the rat cerulein-induced pancreatitis model; however, in that study, NF-kB activation was only measured at one time point and only in vivo, not ex vivo[119]. Of note, CCK-elicited responses in PI3Kγ-null isolated acini were further inhibited by LY294002, implicating involvement of other PI3K isoforms[127].

Our research group independently studied the effects of genetic ablation of PI3Kγ on the severity of acute pancreatic damage induced in vivo by supramaximally stimulating doses of cerulein or administration of a choline-deficient, ethionine-supplemented (CDE) diet[126]. Although amylase secretion in isolated pancreatic acini was not different in PI3Kγ-null mice compared to wild-type mice, the genetic ablation had significantly reduced the extent of acinar cell injury/necrosis in both models. A partial but significant reduction in the extent of acinar cell injury/necrosis was evident six hours after the beginning of cerulein administration. On the contrary, serum amylase levels were not decreased and pancreatic water content was even increased in the PI3Kγ-deficient mice compared to the wild-type mice. In addition, only minimal neutrophil infiltration was seen at time points as early as six hours. Therefore, this protective effect can likely be ascribed to the lack of PI3Kγ influence on the early intra-acinar cell events, as indicated elsewhere[123]. Our study also showed an increase in the number of apoptotic acinar cells in PI3Kγ-null mice (identified by terminal dUTP nick-end labeling and caspase-3 activity), which is consistent with the described protective role of apoptosis in acute pancreatitis[123,126]. As we did not observe any activation of Akt/PKB, the major effector of PI3K survival signaling[127,128], it can be hypothesized that PI3Kγ may interfere with other death signaling pathways, such as caspase activation, cytochrome c release, or mitochondrial depolarization, which have been implicated in the direct pro-apoptotic effect exerted by supramaximal concentrations of CCK in pancreatic acini[119].

We also observed a significant reduction of both acinar cell injury/necrosis and neutrophil infiltration in PI3Kγ-null mice after prolonged administration of cerulein for 13 h[125]. This protective effect may be related to the ability of PI3Kγ to regulate the neutrophil chemotaxis and respiratory burst that follows neutrophil activation[44-48] or to enhance neutrophil apoptosis, thus favoring the removal of activated neutrophils from the pancreatic tissue[130]. Moreover, cerulein-induced pancreatic COX-2 up-regulation, which modulates the course of acute pancreatitis[131,132], was also blunted in the PI3Kγ-null mice, likely contributing to the observed protective effect of genetic ablation[124].

PI3Kγ deletion was also found to reduce acinar cell injury/necrosis, neutrophil infiltration and lung injury in a second model of necrotizing acute pancreatitis induced by administration of a CDE diet[124]. Furthermore, the genetic ablation reduced the mortality rate, indicating that PI3Kγ influences the development of injury to other organs, in particular the lungs. Indeed, a recent study by another group has shown that the PI3K-Akt pathway mediates the protective effect exerted by estrogens on lung injury during cerulein-induced acute pancreatitis[134], indirectly confirming our hypothesis.

PI3Kγ is also known to possess scaffold functions that regulate cAMP levels[72,133], and it can bind protein kinase A (PKA) and different phosphodiesterases[136] to control a PKA-mediated negative feedback signal that promotes cAMP destruction. Given the importance of cAMP elevation in the protection from acute pancreatitis[137], it is therefore possible that some of the effects of PI3Kγ are independent of its catalytic activity.

**CONCLUSION**

The activation of PI3Ks, and in particular of the class IB PI3Kγ isoform, has a relevant role in the biochemical events, namely calcium signaling alteration, trypsinogen activation, and NF-κB transcription, all of which are necessary for the initiation of acute pancreatic injury. The ability of PI3Kγ to modulate acinar cell apoptosis, as well as to regulate local neutrophil infiltration and systemic inflammatory responses during the course of acute pancreatitis, renders PI3Kγ an ideal therapeutic target. The availability of inhibitors selective for specific PI3K isoforms might provide new valuable therapeutic strategies to improve the clinical course of this disease.

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