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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 PI3Kδ 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 the course of experimental acute pancreatitis. The availability of PI3K inhibitors selective for specific isoforms may provide new valuable therapeutic strategies 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.

Key words: Phosphoinositide 3-kinase; Cell signaling; Inflammation; Pathogenesis; Acute pancreatitis

Core tip: Phosphoinositide 3-kinases (PI3Ks) are a family of lipid and protein kinases implicated in intracellular signal transduction and regulation of inflammation. Recent data suggest their involvement also in the pathogenesis of acute pancreatitis. PI3Ks, and in particular the PI3Kγ isoform, have 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 modulates acinar cell apoptosis, and regulates local and systemic inflammatory responses during experimental acute pancreatitis. Specific PI3K inhibitors may therefore provide new therapies to improve the clinical course of this disease.

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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[1,2]. Recent research efforts have begun to clarify the biochemical mechanisms inducing intracellular zymogen activation[3-7], 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[1-3]. Intracellular zymogen activation results in acinar cell necrosis and local inflammatory responses[8], which progressively resolve in most patients[9]. 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[9-14].

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[9,15,16]. Increased levels of circulating inflammatory cytokines, chemokines and other humoral mediators have been reported in patients with acute pancreatitis[17,18], as well as in experimental *in vivo* and *ex vivo* (hyperstimulated acinar cells) models of the disease condition[3,6,14,19-22]. 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[6,22-27]. 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[9,15,16]. Furthermore, experimental anti-inflammatory approaches - ranging from genetic deletion of cytokine receptors[28] or specific integrins[29,30], neutralization of cytokines, chemokines, adhesion molecules or other mediators[18,19,30-36], blockade of neutrophil recruitment[29,35-39], or complement inhibition[40] - 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[14,16,41-43]. 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[44-48]. 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[49,50]. They possess both protein and lipid kinase activity, with the latter function being the most extensively studied[45-47]. PI3Ks have historically been divided into three classes based on protein structure and substrate specificity[45-47].

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[45-47]. Class I PI3Ks have been further divided in two subgroups: IA and IB[45-47]. 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[51], platelet-derived growth factor[52], fibroblast growth factor[53], growth hormone[54,55], insulin-like growth factor[56], insulin[57] and many interleukins (ILs)[58]. 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[59,60]. 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[61,62]. 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[63-65]. 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[45-47]. PI3Kγ is activated by direct binding with G-protein βγ subunits, thus signaling downstream of GPCRs, such as chemokine receptors[45-47]. Moreover, PI3Kγ signaling activity can further be potentiated by Ras-GTP[66]. 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 (PIP_3)[45-47,67,68]. PIP_3, upon membrane translocation, binds

with high affinity to the pleckstrin homology (PH) domain of its many effectors[45-47]. 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 homoeostasis, and cell survival[45-47]. The signaling activity of class I PI3K 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 PIP_3 on position 5 or 3[69-71].

The tissue distribution of class I PI3K isoforms is quite different: PI3Kα and PI3Kβ are widely expressed[45-47], whereas PI3Kγ and PI3Kδ are mainly expressed in leukocytes[44-47]. However, the expression of PI3Kγ has also been reported in the heart and in the endothelium[72,73], as well as in breast and pancreatic cancers[74-76]. Analogously, PI3Kδ expression has also been demonstrated in neurons, and in melanoma and breast cancer cells[77,78].

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[45-47,79,80]. 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[45-47,79,80]. For example, class Ⅱ PI3K-C2α has been demonstrated as critically required for endocytosis[81] and for vascular integrity[82]. Interestingly, PI3K-C2γ is expressed in the exocrine pancreas[83], but its role in this organ remains largely unknown.

Finally, class Ⅲ PI3K includes only one member, vacuolar protein sorting 34 (VSP34), which is only able to generate phosphatidylinositol 3-phosphate[45-47,80]. The physiologic importance of VSP34 and/or its involvement in human pathology are currently unclear[45-47,80].

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[45-48,79,80].

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[45-47]. Genetic ablation of PI3Kα and PI3Kβ was lethal during embryonic development[84,85]; however, PI3Kδ and PI3Kγ knock-out mice were viable and mainly showed alterations of both innate and adaptive immune responses[86-89]. Ultimately, those 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[44-47]. In 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[72,86-88]. In addition, *in vivo* investigation of a peritonitis mouse model showed highly impaired leukocyte recruitment[86-88]. On the contrary, PI3Kδ appears to be specifically involved in regulating the directional neutrophil movement in response to chemotactic agents[90,91]. Endothelial activity of both PI3Kγ and PI3Kδ also has a role in regulating neutrophil adhesion to inflamed vessel wall[91,92]. 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[86-88,90,91].

In addition to the roles of PI3Ks in neutrophils and monocytes, these kinases also regulate fundamental cellular functions in mast cells and eosinophils[45-47]. Pharmacological inhibition of PI3Kδ reduces degranulation and cytokine release induced in mast cells by immunoglobulin (Ig)E stimulation[93,94] and protects mice from passive cutaneous anaphylaxis induced by IgE and antigen injection[93,94]. In addition, inhibition of PI3Kγ decreases adenosine-induced mast cell degranulation and resistance to passive systemic anaphylaxis[95], demonstrating a specific role for this kinase in sustaining and maximizing mast cell degranulation[93,95]. Furthermore, PI3Kγ is involved in eosinophil recruitment, modulation of allergen-induced eosinophilic airway inflammation, and airway remodeling[96,97].

PI3K activity is also involved in regulation of the cellular functions of T and B lymphocytes, the main actors of the adaptive immune response[45-47]. Both PI3Kγ and PI3Kδ are considered crucial for T cell development[45-47], 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[87,98,99]. Moreover, PI3Kδ is heavily involved in $CD4^+$ T cell maturation and differentiation in distinct T cell subsets[45-47,61], whereas PI3Kγ is involved in T cell receptor-stimulated proliferation and cytokine production[61,87]. PI3Kδ is also involved in the regulation of B cell maturation and activation[45-47]. 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[89,100,101], as well as reduced IgM and IgG antibody responses, which were associated with a paradoxical increase in production of IgE[89,102,103]. 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[104].

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[44-48].

Blockade of PI3Kγ by genetic ablation or by using selective pharmacological inhibitors reduces the incidence and severity of disease in the MRL-lpr mouse model of systemic lupus erythematous[105] 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[108].

Consistent with the role of PI3Ks in mast cell and eosinophil activation[93-97], genetic ablation of PI3Kγ reduces leukocyte infiltration, hyper-responsiveness, and airway remodeling in an ovalbumin (OVA)-induced model of asthma[96,97,109]. 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), bronchiolar 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]. PI3Kγ 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 PI3Kγ-null mice into $LDLR^{-/-}$ mice also reduces plaque size[113], indicating that the formation of atherosclerotic lesions is regulated by PI3Kγ expressed by immune cells. Moreover, PI3Kγ 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 PI3Kγ 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]. However, pharmacologic analysis has implicated PI3Ks in cholecystokinin (CCK)-induced phosphorylation of p70S6 kinase and focal adhesion kinase and in regulation of exocytosis[115-118].

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. *Ex 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[119]. 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_3, nor did they induce phosphorylation of Akt/PKB in these 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 cerulean[120]. 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 PI3Kγ isoform in the pathogenesis of acute pancreatitis. Gukovsky *et al*[121] used PI3Kγ-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 PI3Kγ genetic ablation and PI3K inhibition greatly diminished the CCK-induced calcium response in pancreatic acini by inhibiting both intracellular calcium mobilization and calcium influx, showing that PI3Kγ is required for pathologic calcium responses to CCK hyperstimulation[121]. Further studies by the same group demonstrated that PI3Kγ regulates calcium signaling in pancreatic acinar cells by inhibiting sarco(endo)plasmic reticulum calcium-ATPase[122,123]. In addition to its regulatory role on calcium signaling, PI3Kγ 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[121], an effect that may also be partially mediated through calcium signaling[121]. Finally, both PI3K inhibitors and PI3Kγ genetic deletion inhibited CCK-induced NF-κB activation *in vitro*, indicating a regulatory role for PI3Kγ in the NF-κB response[121]. 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-κB 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[121].

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[124]. 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[121]. 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[125,126]. 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[129].

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[124]. 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[131-133], 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[72,135], 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.

REFERENCES

1 **Sah RP**, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. *Curr Opin Gastroenterol* 2013; **29**: 523-530 [PMID: 23892538 DOI: 10.1097/MOG.0b013e328363e399]

2 **Sah RP**, Garg P, Saluja AK. Pathogenic mechanisms of acute pancreatitis. *Curr Opin Gastroenterol* 2012; **28**: 507-515 [PMID: 22885948 DOI: 10.1097/MOG.0b013e3283567f52]

3 **Saluja AK**, Lerch MM, Phillips PA, Dudeja V. Why does pancreatic overstimulation cause pancreatitis? *Annu Rev Physiol* 2007; **69**: 249-269 [PMID: 17059357 DOI: 10.1146/annurev.physiol.69.031905.161253]

4 **Gorelick FS**, Thrower E. The acinar cell and early pancreatitis responses. *Clin Gastroenterol Hepatol* 2009; **7**: S10-S14 [PMID: 19896090 DOI: 10.1016/j.cgh.2009.07.036]

5 **Hofbauer B**, Saluja AK, Lerch MM, Bhagat L, Bhatia M, Lee HS, Frossard JL, Adler G, Steer ML. Intra-acinar cell activation of trypsinogen during caerulein-induced pancreatitis in rats. *Am J Physiol* 1998; **275**: G352-G362 [PMID: 9688663]

6 **Gukovsky I**, Gukovskaya AS, Blinman TA, Zaninovic V, Pandol SJ. Early NF-kappaB activation is associated with hormone-induced pancreatitis. *Am J Physiol* 1998; **275**: G1402-G1414 [PMID: 9843778]

7 **Hietaranta AJ**, Saluja AK, Bhagat L, Singh VP, Song AM, Steer ML. Relationship between NF-kappaB and trypsinogen activation in rat pancreas after supramaximal caerulein stimulation. *Biochem Biophys Res Commun* 2001; **280**: 388-395 [PMID: 11162528 DOI: 10.1006/bbrc.2000.4120]

8 **Hoque R**, Malik AF, Gorelick F, Mehal WZ. Sterile inflammatory response in acute pancreatitis. *Pancreas* 2012; **41**: 353-357 [PMID: 22415665 DOI: 10.1097/MPA.0b013e3182321500]

9 **Frossard JL**, Steer ML, Pastor CM. Acute pancreatitis. *Lancet* 2008; **371**: 143-152 [PMID: 18191686 DOI: 10.1016/S0140-6736(08)60107-5]

10 **Buter A**, Imrie CW, Carter CR, Evans S, McKay CJ. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg* 2002; **89**: 298-302 [PMID: 11872053 DOI: 10.1046/j.0007-1323.2001.02025.x]

11 **Mofidi R**, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg* 2006; **93**: 738-744 [PMID: 16671062 DOI: 10.1002/bjs.5290]

12 **Pandol SJ**, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. *Gastroenterology* 2007; **132**: 1127-1151 [PMID: 17383433 DOI: 10.1053/j.gastro.2007.01.055]

13 **Singh VK**, Wu BU, Bollen TL, Repas K, Maurer R, Mortele KJ, Banks PA. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1247-1251 [PMID: 19686869 DOI: 10.1016/j.cgh.2009.08.012]

14 **Bhatia M**, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J. Inflammatory mediators in acute pancreatitis. *J Pathol* 2000; **190**: 117-125 [PMID: 10657008 DOI: 10.1002/(SICI)1096-9896(200002)190:2<117::AID-PATH494>3.0.CO;2-K]

15 **Gukovsky I**, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; **144**: 1199-1209.e4 [PMID: 23622129 DOI: 10.1053/j.gastro.2013.02.007]

16 **Kylänpää ML**, Repo H, Puolakkainen PA. Inflammation and immunosuppression in severe acute pancreatitis. *World J Gastroenterol* 2010; **16**: 2867-2872 [PMID: 20556831 DOI: 10.3748/wjg.v16.i23.2867]

17 **Leser HG**, Gross V, Scheibenbogen C, Heinisch A, Salm R, Lausen M, Rückauer K, Andreesen R, Farthmann EH, Schölmerich J. Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. *Gastroenterology* 1991; **101**: 782-785 [PMID: 1907253]

18 **Norman J**. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 1998; **175**: 76-83 [PMID: 9445247 DOI: 10.1016/S0002-9610(97)00240-7]

19 **Gukovskaya AS**, Gukovsky I, Zaninovic V, Song M, Sandoval D, Gukovsky S, Pandol SJ. Pancreatic acinar cells produce, release, and respond to tumor necrosis factor-alpha. Role in regulating cell death and pancreatitis. *J Clin Invest* 1997; **100**: 1853-1862 [PMID: 9312187 DOI: 10.1172/JCI119714]

20 **Grady T**, Liang P, Ernst SA, Logsdon CD. Chemokine gene expression in rat pancreatic acinar cells is an early event associated with acute pancreatitis. *Gastroenterology* 1997; **113**: 1966-1975 [PMID: 9394737 DOI: 10.1016/S0016-5085(97)70017-9]

21 **Orlichenko LS**, Behari J, Yeh TH, Liu S, Stolz DB, Saluja AK, Singh VP. Transcriptional regulation of CXC-ELR chemokines KC and MIP-2 in mouse pancreatic acini. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G867-G876 [PMID: 20671197 DOI: 10.1152/ajpgi.00177.2010]

22 **Vaquero E**, Gukovsky I, Zaninovic V, Gukovskaya AS, Pandol SJ. Localized pancreatic NF-kappaB activation and inflammatory response in taurocholate-induced pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G1197-G1208 [PMID: 11352813]

23 **Steinle AU**, Weidenbach H, Wagner M, Adler G, Schmid RM. NF-kappaB/Rel activation in cerulein pancreatitis. *Gastroenterology* 1999; **116**: 420-430 [PMID: 9922324 DOI: 10.1016/S0016-5085(99)70140-X]

24 **Chen X**, Ji B, Han B, Ernst SA, Simeone D, Logsdon CD. NF-kappaB activation in pancreas induces pancreatic and systemic inflammatory response. *Gastroenterology* 2002; **122**: 448-457 [PMID: 11832459 DOI: 10.1053/gast.2002.31060]

25 **Altavilla D**, Famulari C, Passaniti M, Galeano M, Macrì A, Seminara P, Minutoli L, Marini H, Calò M, Venuti FS, Esposito M, Squadrito F. Attenuated cerulein-induced pancreatitis in nuclear factor-kappaB-deficient mice. *Lab Invest* 2003; **83**: 1723-1732 [PMID: 14691290 DOI: 10.1097/01.LAB.0000101734.82054.BE]

26 **Huang H**, Liu Y, Daniluk J, Gaiser S, Chu J, Wang H, Li ZS, Logsdon CD, Ji B. Activation of nuclear factor-κB in acinar cells increases the severity of pancreatitis in mice. *Gastroenterology* 2013; **144**: 202-210 [PMID: 23041324 DOI: 10.1053/j.gastro.2012.09.059]

27 **Gukovsky I**, Gukovskaya A. Nuclear factor-κB in pancreatitis: Jack-of-all-trades, but which one is more important? *Gastroenterology* 2013; **144**: 26-29 [PMID: 23164573 DOI: 10.1053/j.gastro.2012.11.016]

28 **Denham W**, Yang J, Fink G, Denham D, Carter G, Ward K, Norman J. Gene targeting demonstrates additive detrimental effects of interleukin 1 and tumor necrosis factor during pancreatitis. *Gastroenterology* 1997; **113**: 1741-1746 [PMID: 9352880 DOI: 10.1053/gast.1997.v113.pm9352880]

29 **Awla D**, Abdulla A, Zhang S, Roller J, Menger MD, Regnér S, Thorlacius H. Lymphocyte function antigen-1 regulates neutrophil recruitment and tissue damage in acute pancreatitis. *Br J Pharmacol* 2011; **163**: 413-423 [PMID: 21244370 DOI: 10.1111/j.1476-5381.2011.01225.x]

30 **Sendler M**, Dummer A, Weiss FU, Krüger B, Wartmann T, Scharffetter-Kochanek K, van Rooijen N, Malla SR, Aghdassi A, Halangk W, Lerch MM, Mayerle J. Tumour necrosis factor α secretion induces protease activation and acinar cell necrosis in acute experimental pancreatitis in mice. *Gut* 2013; **62**: 430-439 [PMID: 22490516 DOI: 10.1136/gutjnl-2011-300771]

31 **Awla D**, Abdulla A, Syk I, Jeppsson B, Regnér S, Thorlacius H. Neutrophil-derived matrix metalloproteinase-9 is a potent activator of trypsinogen in acinar cells in acute pancreatitis. *J Leukoc Biol* 2012; **91**: 711-719 [PMID: 22100390 DOI: 10.1189/jlb.0811443]

32 **Frossard JL**, Lenglet S, Montecucco F, Steffens S, Galan K, Pelli G, Spahr L, Mach F, Hadengue A. Role of CCL-2, CCR-2 and CCR-4 in cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *J Clin Pathol* 2011; **64**: 387-393 [PMID: 21345872 DOI: 10.1136/jcp.2010.088500]

33 **Sakai Y**, Masamune A, Satoh A, Nishihira J, Yamagiwa T, Shimosegawa T. Macrophage migration inhibitory factor is a critical mediator of severe acute pancreatitis. *Gastroenterology* 2003; **124**: 725-736 [PMID: 12612911 DOI: 10.1053/gast.2003.50099]

34 **Zaninovic V**, Gukovskaya AS, Gukovsky I, Mouria M, Pandol SJ. Cerulein upregulates ICAM-1 in pancreatic acinar cells, which mediates neutrophil adhesion to these cells. *Am J Physiol Gastrointest Liver Physiol* 2000; **279**: G666-G676 [PMID: 11005752]

35 **Hartman H**, Abdulla A, Awla D, Lindkvist B, Jeppsson B, Thorlacius H, Regnér S. P-selectin mediates neutrophil rolling and recruitment in acute pancreatitis. *Br J Surg* 2012; **99**: 246-255 [PMID: 22109627 DOI: 10.1002/bjs.7775]

36 **Frossard JL**, Saluja A, Bhagat L, Lee HS, Bhatia M, Hofbauer B, Steer ML. The role of intercellular adhesion molecule 1 and neutrophils in acute pancreatitis and pancreatitis-associated lung injury. *Gastroenterology* 1999; **116**: 694-701 [PMID: 10029629 DOI: 10.1016/S0016-5085(99)70192-7]

37 **Sandoval D**, Gukovskaya A, Reavey P, Gukovsky S, Sisk A, Braquet P, Pandol SJ, Poucell-Hatton S. The role of neutrophils and platelet-activating factor in mediating experimental pancreatitis. *Gastroenterology* 1996; **111**: 1081-1091 [PMID: 8831604 DOI: 10.1016/S0016-5085(96)70077-X]

38 **Gukovskaya AS**, Vaquero E, Zaninovic V, Gorelick FS, Lu-

sis AJ, Brennan ML, Holland S, Pandol SJ. Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. *Gastroenterology* 2002; **122**: 974-984 [PMID: 11910350 DOI: 10.1053/gast.2002.32409]

39 **Abdulla A**, Awla D, Thorlacius H, Regnér S. Role of neutrophils in the activation of trypsinogen in severe acute pancreatitis. *J Leukoc Biol* 2011; **90**: 975-982 [PMID: 21810937 DOI: 10.1189/jlb.0411195]

40 **Hartwig W**, Klafs M, Kirschfink M, Hackert T, Schneider L, Gebhard MM, Büchler MW, Werner J. Interaction of complement and leukocytes in severe acute pancreatitis: potential for therapeutic intervention. *Am J Physiol Gastrointest Liver Physiol* 2006; **291**: G844-G850 [PMID: 17030899 DOI: 10.1152/ajpgi.00016.2006]

41 **Frossard JL**, Morel P, Pastor CM. Why clinical trials might succeed in acute pancreatitis when they failed in septic shock. *JOP* 2003; **4**: 11-16 [PMID: 12555010]

42 **Pezzilli R**, Ceciliato R, Barakat B, Corinaldesi R. Immune-manipulation of the inflammatory response in acute pancreatitis. What can be expected? *JOP* 2004; **5**: 115-121 [PMID: 15138332]

43 **Bang UC**, Semb S, Nojgaard C, Bendtsen F. Pharmacological approach to acute pancreatitis. *World J Gastroenterol* 2008; **14**: 2968-2976 [PMID: 18494044 DOI: 10.3748/wjg.14.2968]

44 **Wymann MP**, Sozzani S, Altruda F, Mantovani A, Hirsch E. Lipids on the move: phosphoinositide 3-kinases in leukocyte function. *Immunol Today* 2000; **21**: 260-264 [PMID: 10939787 DOI: 10.1016/S0167-5699(00)01649-2]

45 **Foster JG**, Blunt MD, Carter E, Ward SG. Inhibition of PI3K signaling spurs new therapeutic opportunities in inflammatory/autoimmune diseases and hematological malignancies. *Pharmacol Rev* 2012; **64**: 1027-1054 [PMID: 23023033 DOI: 10.1124/pr.110.004051]

46 **Fougerat A**, Gayral S, Malet N, Briand-Mesange F, Breton-Douillon M, Laffargue M. Phosphoinositide 3-kinases and their role in inflammation: potential clinical targets in atherosclerosis? *Clin Sci* (Lond) 2009; **116**: 791-804 [PMID: 19397491 DOI: 10.1042/CS20080549]

47 **Ghigo A**, Damilano F, Braccini L, Hirsch E. PI3K inhibition in inflammation: Toward tailored therapies for specific diseases. *Bioessays* 2010; **32**: 185-196 [PMID: 20162662 DOI: 10.1002/bies.200900150]

48 **Blunt MD**, Ward SG. Pharmacological targeting of phosphoinositide lipid kinases and phosphatases in the immune system: success, disappointment, and new opportunities. *Front Immunol* 2012; **3**: 226 [PMID: 22876243 DOI: 10.3389/fimmu.2012.00226]

49 **Whitman M**, Downes CP, Keeler M, Keller T, Cantley L. Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature* 1988; **332**: 644-646 [PMID: 2833705 DOI: 10.1038/332644a0]

50 **Courtneidge SA**, Heber A. An 81 kd protein complexed with middle T antigen and pp60c-src: a possible phosphatidylinositol kinase. *Cell* 1987; **50**: 1031-1037 [PMID: 2441879 DOI: 10.1016/0092-8674(87)90169-3]

51 **Yart A**, Laffargue M, Mayeux P, Chretien S, Peres C, Tonks N, Roche S, Payrastre B, Chap H, Raynal P. A critical role for phosphoinositide 3-kinase upstream of Gab1 and SHP2 in the activation of ras and mitogen-activated protein kinases by epidermal growth factor. *J Biol Chem* 2001; **276**: 8856-8864 [PMID: 11134009 DOI: 10.1074/jbc.M006966200]

52 **Kazlauskas A**, Cooper JA. Phosphorylation of the PDGF receptor beta subunit creates a tight binding site for phosphatidylinositol 3 kinase. *EMBO J* 1990; **9**: 3279-3286 [PMID: 2170111]

53 **Kanda S**, Hodgkin MN, Woodfield RJ, Wakelam MJ, Thomas G, Claesson-Welsh L. Phosphatidylinositol 3′-kinase-independent p70 S6 kinase activation by fibroblast growth factor receptor-1 is important for proliferation but not differentiation of endothelial cells. *J Biol Chem* 1997; **272**: 23347-23353 [PMID: 9287347 DOI: 10.1074/jbc.272.37.23347]

54 **Campbell GS**. Growth-hormone signal transduction. *J Pediatr* 1997; **131**: S42-S44 [PMID: 9255227 DOI: 10.1016/S0022-3476(97)70010-6]

55 **Argetsinger LS**, Hsu GW, Myers MG, Billestrup N, White MF, Carter-Su C. Growth hormone, interferon-gamma, and leukemia inhibitory factor promoted tyrosyl phosphorylation of insulin receptor substrate-1. *J Biol Chem* 1995; **270**: 14685-14692 [PMID: 7782332 DOI: 10.1074/jbc.270.24.14685]

56 **Yamamoto K**, Altschuler D, Wood E, Horlick K, Jacobs S, Lapetina EG. Association of phosphorylated insulin-like growth factor-I receptor with the SH2 domains of phosphatidylinositol 3-kinase p85. *J Biol Chem* 1992; **267**: 11337-11343 [PMID: 1317864]

57 **Backer JM**, Myers MG, Shoelson SE, Chin DJ, Sun XJ, Miralpeix M, Hu P, Margolis B, Skolnik EY, Schlessinger J. Phosphatidylinositol 3′-kinase is activated by association with IRS-1 during insulin stimulation. *EMBO J* 1992; **11**: 3469-3479 [PMID: 1380456]

58 **Wymann MP**, Zvelebil M, Laffargue M. Phosphoinositide 3-kinase signalling--which way to target? *Trends Pharmacol Sci* 2003; **24**: 366-376 [PMID: 12871670 DOI: 10.1016/S0165-6147(03)00163-9]

59 **Foukas LC**, Claret M, Pearce W, Okkenhaug K, Meek S, Peskett E, Sancho S, Smith AJ, Withers DJ, Vanhaesebroeck B. Critical role for the p110alpha phosphoinositide-3-OH kinase in growth and metabolic regulation. *Nature* 2006; **441**: 366-370 [PMID: 16625210 DOI: 10.1038/nature04694]

60 **Knight ZA**, Gonzalez B, Feldman ME, Zunder ER, Goldenberg DD, Williams O, Loewith R, Stokoe D, Balla A, Toth B, Balla T, Weiss WA, Williams RL, Shokat KM. A pharmacological map of the PI3-K family defines a role for p110alpha in insulin signaling. *Cell* 2006; **125**: 733-747 [PMID: 16647110 DOI: 10.1016/j.cell.2006.03.035]

61 **Fruman DA**. Phosphoinositide 3-kinase and its targets in B-cell and T-cell signaling. *Curr Opin Immunol* 2004; **16**: 314-320 [PMID: 15134780 DOI: 10.1016/j.coi.2004.03.014]

62 **Chen K**, Iribarren P, Gong W, Wang JM. The essential role of phosphoinositide 3-kinases (PI3Ks) in regulating pro-inflammatory responses and the progression of cancer. *Cell Mol Immunol* 2005; **2**: 241-252 [PMID: 16274621]

63 **Guillermet-Guibert J**, Bjorklof K, Salpekar A, Gonella C, Ramadani F, Bilancio A, Meek S, Smith AJ, Okkenhaug K, Vanhaesebroeck B. The p110beta isoform of phosphoinositide 3-kinase signals downstream of G protein-coupled receptors and is functionally redundant with p110gamma. *Proc Natl Acad Sci USA* 2008; **105**: 8292-8297 [PMID: 18544649 DOI: 10.1073/pnas.0707761105]

64 **Ciraolo E**, Iezzi M, Marone R, Marengo S, Curcio C, Costa C, Azzolino O, Gonella C, Rubinetto C, Wu H, Dastrù W, Martin EL, Silengo L, Altruda F, Turco E, Lanzetti L, Musiani P, Rückle T, Rommel C, Backer JM, Forni G, Wymann MP, Hirsch E. Phosphoinositide 3-kinase p110beta activity: key role in metabolism and mammary gland cancer but not development. *Sci Signal* 2008; **1**: ra3 [PMID: 18780892 DOI: 10.1126/scisignal.1161577]

65 **Jia S**, Liu Z, Zhang S, Liu P, Zhang L, Lee SH, Zhang J, Signoretti S, Loda M, Roberts TM, Zhao JJ. Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. *Nature* 2008; **454**: 776-779 [PMID: 18594509 DOI: 10.1038/nature07091]

66 **Germena G**, Hirsch E. PI3Ks and small GTPases in neutrophil migration: two sides of the same coin. *Mol Immunol* 2013; **55**: 83-86 [PMID: 23137593 DOI: 10.1016/j.molimm.2012.10.004]

67 **Pirola L**, Zvelebil MJ, Bulgarelli-Leva G, Van Obberghen E, Waterfield MD, Wymann MP. Activation loop sequences confer substrate specificity to phosphoinositide 3-kinase alpha (PI3Kalpha). Functions of lipid kinase-deficient PI3Kal-

pha in signaling. *J Biol Chem* 2001; **276**: 21544-21554 [PMID: 11278889 DOI: 10.1074/jbc.M011330200]
68 **Bondeva T**, Pirola L, Bulgarelli-Leva G, Rubio I, Wetzker R, Wymann MP. Bifurcation of lipid and protein kinase signals of PI3Kgamma to the protein kinases PKB and MAPK. *Science* 1998; **282**: 293-296 [PMID: 9765155 DOI: 10.1126/science.282.5387.293]
69 **Rohrschneider LR**, Fuller JF, Wolf I, Liu Y, Lucas DM. Structure, function, and biology of SHIP proteins. *Genes Dev* 2000; **14**: 505-520 [PMID: 10716940]
70 **Wishart MJ**, Dixon JE. PTEN and myotubularin phosphatases: from 3-phosphoinositide dephosphorylation to disease. *Trends Cell Biol* 2002; **12**: 579-585 [PMID: 12495846 DOI: 10.1016/S0962-8924(02)02412-1]
71 **Harris SJ**, Parry RV, Westwick J, Ward SG. Phosphoinositide lipid phosphatases: natural regulators of phosphoinositide 3-kinase signaling in T lymphocytes. *J Biol Chem* 2008; **283**: 2465-2469 [PMID: 18073217 DOI: 10.1074/jbc.R700044200]
72 **Patrucco E**, Notte A, Barberis L, Selvetella G, Maffei A, Brancaccio M, Marengo S, Russo G, Azzolino O, Rybalkin SD, Silengo L, Altruda F, Wetzker R, Wymann MP, Lembo G, Hirsch E. PI3Kgamma modulates the cardiac response to chronic pressure overload by distinct kinase-dependent and -independent effects. *Cell* 2004; **118**: 375-387 [PMID: 15294162 DOI: 10.1016/j.cell.2004.07.017]
73 **Crackower MA**, Oudit GY, Kozieradzki I, Sarao R, Sun H, Sasaki T, Hirsch E, Suzuki A, Shioi T, Irie-Sasaki J, Sah R, Cheng HY, Rybin VO, Lembo G, Fratta L, Oliveira-dos-Santos AJ, Benovic JL, Kahn CR, Izumo S, Steinberg SF, Wymann MP, Backx PH, Penninger JM. Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. *Cell* 2002; **110**: 737-749 [PMID: 12297047 DOI: 10.1016/S0092-8674(02)00969-8]
74 **Edling CE**, Selvaggi F, Buus R, Maffucci T, Di Sebastiano P, Friess H, Innocenti P, Kocher HM, Falasca M. Key role of phosphoinositide 3-kinase class IB in pancreatic cancer. *Clin Cancer Res* 2010; **16**: 4928-4937 [PMID: 20876794 DOI: 10.1158/1078-0432.CCR-10-1210]
75 **Brazzatti JA**, Klingler-Hoffmann M, Haylock-Jacobs S, Harata-Lee Y, Niu M, Higgins MD, Kochetkova M, Hoffmann P, McColl SR. Differential roles for the p101 and p84 regulatory subunits of PI3Kγ in tumor growth and metastasis. *Oncogene* 2012; **31**: 2350-2361 [PMID: 21996737 DOI: 10.1038/onc.2011.414]
76 **Dituri F**, Mazzocca A, Lupo L, Edling CE, Azzariti A, Antonaci S, Falasca M, Giannelli G. PI3K class IB controls the cell cycle checkpoint promoting cell proliferation in hepatocellular carcinoma. *Int J Cancer* 2012; **130**: 2505-2513 [PMID: 21796621 DOI: 10.1002/ijc.26319]
77 **Sawyer C**, Sturge J, Bennett DC, O'Hare MJ, Allen WE, Bain J, Jones GE, Vanhaesebroeck B. Regulation of breast cancer cell chemotaxis by the phosphoinositide 3-kinase p110delta. *Cancer Res* 2003; **63**: 1667-1675 [PMID: 12670921]
78 **Veerasingham SJ**, Yamazato M, Berecek KH, Wyss JM, Raizada MK. Increased PI3-kinase in presympathetic brain areas of the spontaneously hypertensive rat. *Circ Res* 2005; **96**: 277-279 [PMID: 15662030 DOI: 10.1161/01.RES.0000156275.06641.b2]
79 **Falasca M**, Maffucci T. Regulation and cellular functions of class II phosphoinositide 3-kinases. *Biochem J* 2012; **443**: 587-601 [PMID: 22507127 DOI: 10.1042/BJ20120008]
80 **Vanhaesebroeck B**, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. *Nat Rev Mol Cell Biol* 2010; **11**: 329-341 [PMID: 20379207 DOI: 10.1038/nrm2882]
81 **Posor Y**, Eichhorn-Gruenig M, Puchkov D, Schöneberg J, Ullrich A, Lampe A, Müller R, Zarbakhsh S, Gulluni F, Hirsch E, Krauss M, Schultz C, Schmoranzer J, Noé F, Haucke V. Spatiotemporal control of endocytosis by phosphatidylinositol-3,4-bisphosphate. *Nature* 2013; **499**: 233-237 [PMID: 23823722 DOI: 10.1038/nature12360]
82 **Yoshioka K**, Yoshida K, Cui H, Wakayama T, Takuwa N, Okamoto Y, Du W, Qi X, Asanuma K, Sugihara K, Aki S, Miyazawa H, Biswas K, Nagakura C, Ueno M, Iseki S, Schwartz RJ, Okamoto H, Sasaki T, Matsui O, Asano M, Adams RH, Takakura N, Takuwa Y. Endothelial PI3K-C2α, a class II PI3K, has an essential role in angiogenesis and vascular barrier function. *Nat Med* 2012; **18**: 1560-1569 [PMID: 22983395 DOI: 10.1038/nm.2928]
83 **Ho LK**, Liu D, Rozycka M, Brown RA, Fry MJ. Identification of four novel human phosphoinositide 3-kinases defines a multi-isoform subfamily. *Biochem Biophys Res Commun* 1997; **235**: 130-137 [PMID: 9196049 DOI: 10.1006/bbrc.1997.6747]
84 **Bi L**, Okabe I, Bernard DJ, Wynshaw-Boris A, Nussbaum RL. Proliferative defect and embryonic lethality in mice homozygous for a deletion in the p110alpha subunit of phosphoinositide 3-kinase. *J Biol Chem* 1999; **274**: 10963-10968 [PMID: 10196176 DOI: 10.1074/jbc.274.16.10963]
85 **Bi L**, Okabe I, Bernard DJ, Nussbaum RL. Early embryonic lethality in mice deficient in the p110beta catalytic subunit of PI 3-kinase. *Mamm Genome* 2002; **13**: 169-172 [PMID: 11919689 DOI: 10.1007/s00335-001-2123-x]
86 **Hirsch E**, Katanaev VL, Garlanda C, Azzolino O, Pirola L, Silengo L, Sozzani S, Mantovani A, Altruda F, Wymann MP. Central role for G protein-coupled phosphoinositide 3-kinase gamma in inflammation. *Science* 2000; **287**: 1049-1053 [PMID: 10669418 DOI: 10.1126/science.287.5455.1049]
87 **Sasaki T**, Irie-Sasaki J, Jones RG, Oliveira-dos-Santos AJ, Stanford WL, Bolon B, Wakeham A, Itie A, Bouchard D, Kozieradzki I, Joza N, Mak TW, Ohashi PS, Suzuki A, Penninger JM. Function of PI3Kgamma in thymocyte development, T cell activation, and neutrophil migration. *Science* 2000; **287**: 1040-1046 [PMID: 10669416 DOI: 10.1126/science.287.5455.1040]
88 **Li Z**, Jiang H, Xie W, Zhang Z, Smrcka AV, Wu D. Roles of PLC-beta2 and -beta3 and PI3Kgamma in chemoattractant-mediated signal transduction. *Science* 2000; **287**: 1046-1049 [PMID: 10669417 DOI: 10.1126/science.287.5455.1046]
89 **Okkenhaug K**, Bilancio A, Farjot G, Priddle H, Sancho S, Peskett E, Pearce W, Meek SE, Salpekar A, Waterfield MD, Smith AJ, Vanhaesebroeck B. Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice. *Science* 2002; **297**: 1031-1034 [PMID: 12130661 DOI: 10.1126/science.1073560]
90 **Sadhu C**, Masinovsky B, Dick K, Sowell CG, Staunton DE. Essential role of phosphoinositide 3-kinase delta in neutrophil directional movement. *J Immunol* 2003; **170**: 2647-2654 [PMID: 12594293 DOI: 10.4049/jimmunol.170.5.2647]
91 **Puri KD**, Doggett TA, Douangpanya J, Hou Y, Tino WT, Wilson T, Graf T, Clayton E, Turner M, Hayflick JS, Diacovo TG. Mechanisms and implications of phosphoinositide 3-kinase delta in promoting neutrophil trafficking into inflamed tissue. *Blood* 2004; **103**: 3448-3456 [PMID: 14751923 DOI: 10.1182/blood-2003-05-1667]
92 **Puri KD**, Doggett TA, Huang CY, Douangpanya J, Hayflick JS, Turner M, Penninger J, Diacovo TG. The role of endothelial PI3Kgamma activity in neutrophil trafficking. *Blood* 2005; **106**: 150-157 [PMID: 15769890 DOI: 10.1182/blood-2005-01-0023]
93 **Ali K**, Bilancio A, Thomas M, Pearce W, Gilfillan AM, Tkaczyk C, Kuehn N, Gray A, Giddings J, Peskett E, Fox R, Bruce I, Walker C, Sawyer C, Okkenhaug K, Finan P, Vanhaesebroeck B. Essential role for the p110delta phosphoinositide 3-kinase in the allergic response. *Nature* 2004; **431**: 1007-1011 [PMID: 15496927 DOI: 10.1038/nature02991]
94 **Ali K**, Camps M, Pearce WP, Ji H, Rückle T, Kuehn N, Pasquali C, Chabert C, Rommel C, Vanhaesebroeck B. Isoform-specific functions of phosphoinositide 3-kinases: p110 delta but not p110 gamma promotes optimal allergic responses in vivo. *J Immunol* 2008; **180**: 2538-2544 [PMID:

18250464 DOI: 10.4049/jimmunol.180.4.2538]
95 **Laffargue M**, Calvez R, Finan P, Trifilieff A, Barbier M, Altruda F, Hirsch E, Wymann MP. Phosphoinositide 3-kinase gamma is an essential amplifier of mast cell function. *Immunity* 2002; **16**: 441-451 [PMID: 11911828 DOI: 10.1016/S1074-7613(02)00282-0]
96 **Lim DH**, Cho JY, Song DJ, Lee SY, Miller M, Broide DH. PI3K gamma-deficient mice have reduced levels of allergen-induced eosinophilic inflammation and airway remodeling. *Am J Physiol Lung Cell Mol Physiol* 2009; **296**: L210-L219 [PMID: 19028980 DOI: 10.1152/ajplung.90275.2008]
97 **Takeda M**, Ito W, Tanabe M, Ueki S, Kato H, Kihara J, Tanigai T, Chiba T, Yamaguchi K, Kayaba H, Imai Y, Okuyama K, Ohno I, Sasaki T, Chihara J. Allergic airway hyperresponsiveness, inflammation, and remodeling do not develop in phosphoinositide 3-kinase gamma-deficient mice. *J Allergy Clin Immunol* 2009; **123**: 805-812 [PMID: 19232703 DOI: 10.1016/j.jaci.2008.11.047]
98 **Ji H**, Rintelen F, Waltzinger C, Bertschy Meier D, Bilancio A, Pearce W, Hirsch E, Wymann MP, Rückle T, Camps M, Vanhaesebroeck B, Okkenhaug K, Rommel C. Inactivation of PI3Kgamma and PI3Kdelta distorts T-cell development and causes multiple organ inflammation. *Blood* 2007; **110**: 2940-2947 [PMID: 17626838 DOI: 10.1182/blood-2007-04-086751]
99 **Webb LM**, Vigorito E, Wymann MP, Hirsch E, Turner M. Cutting edge: T cell development requires the combined activities of the p110gamma and p110delta catalytic isoforms of phosphatidylinositol 3-kinase. *J Immunol* 2005; **175**: 2783-2787 [PMID: 16116162 DOI: 10.4049/jimmunol.175.5.2783]
100 **Clayton E**, Bardi G, Bell SE, Chantry D, Downes CP, Gray A, Humphries LA, Rawlings D, Reynolds H, Vigorito E, Turner M. A crucial role for the p110delta subunit of phosphatidylinositol 3-kinase in B cell development and activation. *J Exp Med* 2002; **196**: 753-763 [PMID: 12235209 DOI: 10.1084/jem.20020805]
101 **Jou ST**, Carpino N, Takahashi Y, Piekorz R, Chao JR, Carpino N, Wang D, Ihle JN. Essential, nonredundant role for the phosphoinositide 3-kinase p110delta in signaling by the B-cell receptor complex. *Mol Cell Biol* 2002; **22**: 8580-8591 [PMID: 12446777 DOI: 10.1128/MCB.22.24.8580-8591.2002]
102 **Zhang TT**, Okkenhaug K, Nashed BF, Puri KD, Knight ZA, Shokat KM, Vanhaesebroeck B, Marshall AJ. Genetic or pharmaceutical blockade of p110delta phosphoinositide 3-kinase enhances IgE production. *J Allergy Clin Immunol* 2008; **122**: 811-819.e2 [PMID: 19014771 DOI: 10.1016/j.jaci.2008.08.008]
103 **Omori SA**, Cato MH, Anzelon-Mills A, Puri KD, Shapiro-Shelef M, Calame K, Rickert RC. Regulation of class-switch recombination and plasma cell differentiation by phosphatidylinositol 3-kinase signaling. *Immunity* 2006; **25**: 545-557 [PMID: 17000121 DOI: 10.1016/j.immuni.2006.08.015]
104 **Gopal AK**, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, Flinn IW, Flowers CR, Martin P, Viardot A, Blum KA, Goy AH, Davies AJ, Zinzani PL, Dreyling M, Johnson D, Miller LL, Holes L, Li D, Dansey RD, Godfrey WR, Salles GA. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* 2014; **370**: 1008-1018 [PMID: 24450858 DOI: 10.1056/NEJMoa1314583]
105 **Barber DF**, Bartolomé A, Hernandez C, Flores JM, Redondo C, Fernandez-Arias C, Camps M, Rückle T, Schwarz MK, Rodríguez S, Martinez-A C, Balomenos D, Rommel C, Carrera AC. PI3Kgamma inhibition blocks glomerulonephritis and extends lifespan in a mouse model of systemic lupus. *Nat Med* 2005; **11**: 933-935 [PMID: 16127435 DOI: 10.1038/nm1291]
106 **Camps M**, Rückle T, Ji H, Ardissone V, Rintelen F, Shaw J, Ferrandi C, Chabert C, Gillieron C, Françon B, Martin T, Gretener D, Perrin D, Leroy D, Vitte PA, Hirsch E, Wymann MP, Cirillo R, Schwarz MK, Rommel C. Blockade of PI3Kgamma suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. *Nat Med* 2005; **11**: 936-943 [PMID: 16127437 DOI: 10.1038/nm1284]
107 **Hayer S**, Pundt N, Peters MA, Wunrau C, Kühnel I, Neugebauer K, Strietholt S, Zwerina J, Korb A, Penninger J, Joosten LA, Gay S, Rückle T, Schett G, Pap T. PI3Kgamma regulates cartilage damage in chronic inflammatory arthritis. *FASEB J* 2009; **23**: 4288-4298 [PMID: 19734303 DOI: 10.1096/fj.09-135160]
108 **Randis TM**, Puri KD, Zhou H, Diacovo TG. Role of PI3K-delta and PI3Kgamma in inflammatory arthritis and tissue localization of neutrophils. *Eur J Immunol* 2008; **38**: 1215-1224 [PMID: 18412166]
109 **Thomas M**, Edwards MJ, Sawicka E, Duggan N, Hirsch E, Wymann MP, Owen C, Trifilieff A, Walker C, Westwick J, Finan P. Essential role of phosphoinositide 3-kinase gamma in eosinophil chemotaxis within acute pulmonary inflammation. *Immunology* 2009; **126**: 413-422 [PMID: 18754810 DOI: 10.1111/j.1365-2567.2008.02908.x]
110 **Lee KS**, Lee HK, Hayflick JS, Lee YC, Puri KD. Inhibition of phosphoinositide 3-kinase delta attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model. *FASEB J* 2006; **20**: 455-465 [PMID: 16507763 DOI: 10.1096/fj.05-5045com]
111 **Farghaly HS**, Blagbrough IS, Medina-Tato DA, Watson ML. Interleukin 13 increases contractility of murine tracheal smooth muscle by a phosphoinositide 3-kinase p110delta-dependent mechanism. *Mol Pharmacol* 2008; **73**: 1530-1537 [PMID: 18276774 DOI: 10.1124/mol.108.045419]
112 **Chang JD**, Sukhova GK, Libby P, Schvartz E, Lichtenstein AH, Field SJ, Kennedy C, Madhavarapu S, Luo J, Wu D, Cantley LC. Deletion of the phosphoinositide 3-kinase p110gamma gene attenuates murine atherosclerosis. *Proc Natl Acad Sci USA* 2007; **104**: 8077-8082 [PMID: 17483449 DOI: 10.1073/pnas.0702663104]
113 **Fougerat A**, Gayral S, Gourdy P, Schambourg A, Rückle T, Schwarz MK, Rommel C, Hirsch E, Arnal JF, Salles JP, Perret B, Breton-Douillon M, Wymann MP, Laffargue M. Genetic and pharmacological targeting of phosphoinositide 3-kinase-gamma reduces atherosclerosis and favors plaque stability by modulating inflammatory processes. *Circulation* 2008; **117**: 1310-1317 [PMID: 18268153 DOI: 10.1161/CIRCULATIONAHA.107.720466]
114 **Doukas J**, Wrasidlo W, Noronha G, Dneprovskaia E, Fine R, Weis S, Hood J, Demaria A, Soll R, Cheresh D. Phosphoinositide 3-kinase gamma/delta inhibition limits infarct size after myocardial ischemia/reperfusion injury. *Proc Natl Acad Sci USA* 2006; **103**: 19866-19871 [PMID: 17172449 DOI: 10.1073/pnas.0606956103]
115 **Williams JA**. Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. *Annu Rev Physiol* 2001; **63**: 77-97 [PMID: 11181949 DOI: 10.1146/annurev.physiol.63.1.77]
116 **Bragado MJ**, Groblewski GE, Williams JA. Regulation of protein synthesis by cholecystokinin in rat pancreatic acini involves PHAS-I and the p70 S6 kinase pathway. *Gastroenterology* 1998; **115**: 733-742 [PMID: 9721171 DOI: 10.1016/S0016-5085(98)70153-2]
117 **Rosado JA**, Salido GM, García LJ. A role for phosphoinositides in tyrosine phosphorylation of p125 focal adhesion kinase in rat pancreatic acini. *Cell Signal* 2000; **12**: 173-182 [PMID: 10704824 DOI: 10.1016/S0898-6568(99)00083-2]
118 **Campos-Toimil M**, Bagrij T, Edwardson JM, Thomas P. Two modes of secretion in pancreatic acinar cells: involvement of phosphatidylinositol 3-kinase and regulation by capacitative Ca(2+) entry. *Curr Biol* 2002; **12**: 211-215 [PMID: 11839273 DOI: 10.1016/S0960-9822(01)00661-3]
119 **Singh VP**, Saluja AK, Bhagat L, van Acker GJ, Song AM, Soltoff SP, Cantley LC, Steer ML. Phosphatidylinositol 3-kinase-dependent activation of trypsinogen modulates the se-

verity of acute pancreatitis. *J Clin Invest* 2001; **108**: 1387-1395 [PMID: 11696584 DOI: 10.1172/JCI12874]
120 **Rivard N**, Rydzewska G, Lods JS, Martinez J, Morisset J. Pancreas growth, tyrosine kinase, PtdIns 3-kinase, and PLD involve high-affinity CCK-receptor occupation. *Am J Physiol* 1994; **266**: G62-G70 [PMID: 8304459]
121 **Gukovsky I**, Cheng JH, Nam KJ, Lee OT, Lugea A, Fischer L, Penninger JM, Pandol SJ, Gukovskaya AS. Phosphatidylinositide 3-kinase gamma regulates key pathologic responses to cholecystokinin in pancreatic acinar cells. *Gastroenterology* 2004; **126**: 554-566 [PMID: 14762792 DOI: 10.1053/j.gastro.2003.11.017]
122 **Fischer L**, Gukovskaya AS, Young SH, Gukovsky I, Lugea A, Buechler P, Penninger JM, Friess H, Pandol SJ. Phosphatidylinositol 3-kinase regulates Ca2+ signaling in pancreatic acinar cells through inhibition of sarco(endo)plasmic reticulum Ca2+-ATPase. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G1200-G1212 [PMID: 15271649 DOI: 10.1152/ajpgi.00212.2004]
123 **Fischer L**, Gukovskaya AS, Penninger JM, Mareninova OA, Friess H, Gukovsky I, Pandol SJ. Phosphatidylinositol 3-kinase facilitates bile acid-induced Ca(2+) responses in pancreatic acinar cells. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G875-G886 [PMID: 17158252 DOI: 10.1152/ajpgi.00558.2005]
124 **Lupia E**, Goffi A, De Giuli P, Azzolino O, Bosco O, Patrucco E, Vivaldo MC, Ricca M, Wymann MP, Hirsch E, Montrucchio G, Emanuelli G. Ablation of phosphoinositide 3-kinase-gamma reduces the severity of acute pancreatitis. *Am J Pathol* 2004; **165**: 2003-2011 [PMID: 15579443 DOI: 10.1016/S0002-9440(10)63251-8]
125 **Bhatia M**. Apoptosis of pancreatic acinar cells in acute pancreatitis: is it good or bad? *J Cell Mol Med* 2004; **8**: 402-409 [PMID: 15491516 DOI: 10.1111/j.1582-4934.2004.tb00330.x]
126 **Bhatia M**. Apoptosis versus necrosis in acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G189-G196 [PMID: 14715516 DOI: 10.1152/ajpgi.00304.2003]
127 **Talapatra S**, Thompson CB. Growth factor signaling in cell survival: implications for cancer treatment. *J Pharmacol Exp Ther* 2001; **298**: 873-878 [PMID: 11504779]
128 **Franke TF**, Hornik CP, Segev L, Shostak GA, Sugimoto C. PI3K/Akt and apoptosis: size matters. *Oncogene* 2003; **22**: 8983-8998 [PMID: 14663477 DOI: 10.1038/sj.onc.1207115]
129 **Gukovskaya AS**, Gukovsky I, Jung Y, Mouria M, Pandol SJ. Cholecystokinin induces caspase activation and mitochondrial dysfunction in pancreatic acinar cells. Roles in cell injury processes of pancreatitis. *J Biol Chem* 2002; **277**: 22595-22604 [PMID: 11964411 DOI: 10.1074/jbc.M202929200]
130 **Yum HK**, Arcaroli J, Kupfner J, Shenkar R, Penninger JM, Sasaki T, Yang KY, Park JS, Abraham E. Involvement of phosphoinositide 3-kinases in neutrophil activation and the development of acute lung injury. *J Immunol* 2001; **167**: 6601-6608 [PMID: 11714830 DOI: 10.4049/jimmunol.167.11.6601]
131 **Ethridge RT**, Chung DH, Slogoff M, Ehlers RA, Hellmich MR, Rajaraman S, Saito H, Uchida T, Evers BM. Cyclooxygenase-2 gene disruption attenuates the severity of acute pancreatitis and pancreatitis-associated lung injury. *Gastroenterology* 2002; **123**: 1311-1322 [PMID: 12360491 DOI: 10.1053/gast.2002.35951]
132 **Song AM**, Bhagat L, Singh VP, Van Acker GG, Steer ML, Saluja AK. Inhibition of cyclooxygenase-2 ameliorates the severity of pancreatitis and associated lung injury. *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G1166-G1174 [PMID: 12381531 DOI: 10.1152/ajpgi.00370.2001]
133 **Foitzik T**, Hotz HG, Hotz B, Wittig F, Buhr HJ. Selective inhibition of cyclooxygenase-2 (COX-2) reduces prostaglandin E2 production and attenuates systemic disease sequelae in experimental pancreatitis. *Hepatogastroenterology* 2003; **50**: 1159-1162 [PMID: 12846004]
134 **Yang SJ**, Chen HM, Hsieh CH, Hsu JT, Yeh CN, Yeh TS, Hwang TL, Jan YY, Chen MF. Akt pathway is required for oestrogen-mediated attenuation of lung injury in a rodent model of cerulein-induced acute pancreatitis. *Injury* 2011; **42**: 638-642 [PMID: 20709317 DOI: 10.1016/j.injury.2010.07.242]
135 **Perino A**, Ghigo A, Ferrero E, Morello F, Santulli G, Baillie GS, Damilano F, Dunlop AJ, Pawson C, Walser R, Levi R, Altruda F, Silengo L, Langeberg LK, Neubauer G, Heymans S, Lembo G, Wymann MP, Wetzker R, Houslay MD, Iaccarino G, Scott JD, Hirsch E. Integrating cardiac PIP3 and cAMP signaling through a PKA anchoring function of p110γ. *Mol Cell* 2011; **42**: 84-95 [PMID: 21474070 DOI: 10.1016/j.molcel.2011.01.030]
136 **Ghigo A**, Perino A, Mehel H, Zahradníková A, Morello F, Leroy J, Nikolaev VO, Damilano F, Cimino J, De Luca E, Richter W, Westenbroek R, Catterall WA, Zhang J, Yan C, Conti M, Gomez AM, Vandecasteele G, Hirsch E, Fischmeister R. Phosphoinositide 3-kinase γ protects against catecholamine-induced ventricular arrhythmia through protein kinase A-mediated regulation of distinct phosphodiesterases. *Circulation* 2012; **126**: 2073-2083 [PMID: 23008439 DOI: 10.1161/CIRCULATIONAHA.112.114074]
137 **Sato T**, Otaka M, Odashima M, Kato S, Jin M, Konishi N, Matsuhashi T, Watanabe S. Specific type IV phosphodiesterase inhibitor ameliorates cerulein-induced pancreatitis in rats. *Biochem Biophys Res Commun* 2006; **346**: 339-344 [PMID: 16759642 DOI: 10.1016/j.bbrc.2006.05.133]

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