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Protein Kinase C Isoforms in the Normal Pancreas and in Pancreatic Disease

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Abstract

Protein Kinase C isoforms have been implicated in regulating multiple processes within the healthy pancreas. Moreover, their dysregulation contributes to all aspects of pancreatic disease. In this review, with a focus on acinar, ductal, and islet cells, we highlight the roles and contributions of the different PKC isoforms to normal pancreas function. We also discuss the contribution of PKC enzymes to pancreatic diseases, including insulin resistance and diabetes mellitus, as well as pancreatitis and the development and progression of pancreatic cancer.

Keywords

Protein Kinase C; PKC; pancreas; pancreatitis; pancreatic cancer

1. INTRODUCTION

The protein kinase C (PKC) family consists of ten isoforms that are grouped according to their differing structural characteristics and activation requirements (Figure 1). Each isoform has a similar kinase domain, but their regulatory domains differ, reflecting the different requirements for activation (for a detailed review on PKC structure see [1]). The conventional PKCs (cPKCs) PKC α , PKC β I, PKC β II and PKC γ require diacylglycerol (DAG) to bind to the C1 domain, which contains two Cys-rich motifs, and calcium to bind to the C2 domain. Novel PKCs (nPKCs) PKC δ , PKC ϵ , PKC η and PKC θ require DAG to bind to the C1 domain, but as they lack a C2 domain, there is no requirement for calcium to activate this group. The atypical PKCs PKC ι and PKC ζ have a C1 domain with a single Cys-rich motif, but they lack a C2 domain and are not activated by DAG or calcium. Despite these differences in the regulatory domains of PKCs, there is a pseudosubstrate domain adjacent to the C1 domain in each PKC subgroup. The pseudosubstrate domain prevents phosphorylation of PKC substrates and when this domain is synthetically derived, it can be used as a PKC inhibitor [2].

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PKCs are involved in regulating multiple functions within the healthy pancreas, but also have important roles in pancreatic disease. While a healthy pancreas mainly consists of acini, islets and ductal structures, the composition of these cell types changes dramatically during disease. For example, in patients with insulin resistance and diabetes mellitus, islet cell dysfunction and beta cell death occur as a result of inflammation [3, 4]. Moreover, during pancreatitis, acinar cells can undergo metaplasia to duct-like cells or cell death. In addition, fibrotic tissue and presence of inflammatory cells are a hallmark of this disease [5]. In pancreatic cancer, in addition to pancreatitis-related changes (fibrosis, inflammatory cells), differently-progressed pancreatic duct-like lesions can be detected [6]. In the following we will discuss the roles of PKC molecules in the healthy and abnormal pancreas.

2. PKC IN NORMAL PANCREATIC FUNCTIONS

PKC isoenzymes are key regulators of secretion in the normal pancreas. They regulate hormone secretion in the islets, amylase secretion in acinar cells, and bicarbonate secretion in ductal cells (Figure 2). The known roles and functions of individual PKC isoforms are discussed in more detail in the following.

2.1 Islets

PKC isoforms with the highest expression in human pancreatic islets include PKC α , ϵ , θ , and ζ , although all isoforms have shown some expression [7]. Within alpha cells, which produce glucagon, the most abundant PKC isoforms in mouse are α and $\beta 1$, while η , ϵ , and ζ are most abundant in human alpha cells [8]. In alpha cells, PKC mediates glucagon secretion, as shown by stimulation with the PKC activator PMA, which drove PKC α and δ (human cells; or δ only in mouse cells) to translocate from the cytosol to the plasma membrane and increase glucagon secretion [8, 9]. Additionally, the PKC inhibitor bisindolylmaleimide (BIM) diminishes glucagon secretion [8].

PKC also mediates secretion in beta cells. Expression of PKC isoforms in beta cells includes PKC α , β II, δ , ϵ , ζ , and λ/ι [10]. Within normal tissue, glucose is the main stimulator of insulin release and this is PKC-dependent as evidenced by usage of the pan-PKC inhibitor Ro 31-8220, which blocks the release of insulin [11]. In contrast, the conventional PKC inhibitor Gö6976 does not block glucose-stimulated insulin secretion, suggesting involvement of novel or atypical PKCs in this process [11]. One mechanism to activate PKC in beta cells involves ATP production from the breakdown of glucose, and this increase of ATP causes the closing of K⁺ channels. This results in membrane depolarization and subsequent opening of high voltage-gated calcium (Ca_v) channels, such that the influx of calcium causes PKC activation [12]. Glucose-dependent insulin secretion can also be mediated by PKC in a calcium-independent manner [13]. An additional mechanism of PKC-dependent insulin secretion involves glucagon-like peptide-1 (GLP-1). By activating phospholipase c (PLC), which leads to the production of DAG, GLP-1 activates conventional and novel PKCs [14]. PKC then activates the Na⁺ permeable channels TRPM4 and TRPM5, causing the membrane to depolarize and allowing for an increased rate of action potential firing followed by insulin secretion [14].

PKC also mediates the regulation of oxidative stress in beta cells. Utilizing the GLP-1 agonist exendin-4 (EX4), of which a synthetic peptide has been developed for use in diabetes mellitus type 2 treatment, PKC δ was activated, and promoted antioxidant gene expression [15]. PKC δ phosphorylates Nrf2 at serine residue 40, which triggers release from Kelch-like ECH-associated protein 1 (KEAP1) and translocation of Nrf2 to the nucleus, where it induces expression of antioxidant genes like *GCLC* and *HMOX1* [15].

2.2 Acinar Cells

PKC γ , λ/ι , and ζ are strongly expressed, while PKC α , δ , and θ show weaker expression in human pancreatic acinar cells [7]. Within rat acini, PKC α , δ , ϵ , and ζ have been widely studied [16–18]. Of these isoforms, PKC α , δ , and ϵ undergo translocation to the membrane upon stimulation with physiological levels of cholecystokinin (CCK) [19]. PKC-mediated effects of CCK include amylase secretion, trypsinogen activation, and NF- κ B activation [19, 20].

The pancreatic CCK_A and CCK_B receptors in rodents can exist in different states with high or low binding affinity towards CCK [21, 22]. The low affinity CCK_A receptor state leads to translocation and activation of PKC δ downstream of Src family kinases [23]. While PKC δ was initially described as mediating CCK-induced amylase release [19], further studies used a more specific PKC δ inhibitor, δ V1-1 [24], as well as PKC δ ^{-/-} mice to show that amylase secretion is not dependent on PKC δ expression or activity [20]. The difference in these studies can be explained by the use of rottlerin, which does inhibit amylase secretion [19, 20] and was previously thought to be a specific PKC δ inhibitor, but has since been shown to be a mitochondrial uncoupler that decreases cellular ATP levels [25] and to affect multiple PKC δ -independent pathways [26]. Despite evidence that the PKC δ isoform does not affect amylase secretion, the conventional and novel PKC inhibitor GF109203X does decrease amylase release [19], suggesting an important role for PKC in acinar cell digestive enzyme secretion. Mechanistically, it has been proposed that PKC acts through myristoylated alanine-rich C kinase substrate (MARCKS) to regulate CCK-induced amylase secretion [27]. Upon stimulation with CCK, PKC phosphorylates MARCKS [28], inducing translocation of MARCKS from the plasma membrane to the cytosol [27]. This leads to an increase in amylase secretion, which can be blocked using the PKC inhibitor GF109203X as well as the myristoylated N-terminal sequence of MARCKS (MANS) peptide, which blocks the function of MARCKS [27]. Although the mechanism has not been fully determined, MARCKS translocation is proposed to affect SNAREs [27]. For example, MARCKS associates with GM1a-rich detergent-resistant membrane fractions (DRMs). DRMs contain the t-SNARE Syntaxin2 [27], which likely mediates exocytosis of amylase from acinar cells [29].

Additionally, PKC θ is an important signaling molecule in pancreatic acinar cells that can be activated by CCK [30], as evidenced by phosphorylation at amino-acid residue T538 and translocation from the cytosol to the plasma membrane [31]. This activation occurs through the CCK_A receptor such that most activation occurs through the low affinity state, but about 30% of the activation occurs through the high affinity receptor state [30]. While PKC θ does

not affect amylase release, active PKC θ affects many downstream targets including Src, PYK2, and FAK [30].

2.3 Ductal Systems

PKC α , β , γ , ϵ , ζ , ι , and θ are expressed within human pancreatic ductal systems [7]. In ductal epithelial cells PKC regulates tight junctions, which function as a barrier and separate the apical and basolateral surfaces, thereby maintaining polarity [32]. Through 12-*O*-Tetradecanoylphorbol-13-acetate (TPA)-induced activation of PKC, the tight junction proteins Claudin-18, Claudin-4, Claudin-7, Occludin, Zo-1, and Zo-2 are upregulated [33, 34]. This effect is mitigated by the pan-PKC inhibitor GF109203 and partially-inhibited by PKC isoform-specific inhibitors. Using different PKC inhibitors such as Go6976 (PKC α inhibitor), rottlerin (used as a PKC δ inhibitor) and myristoylated PKC θ pseudosubstrate peptide inhibitor, it was shown that the upregulation of Claudin-4 is dependent on PKC α and the upregulation of Claudin-18 depends on PKC α , δ , and θ , while upregulation of Claudin-7, Occludin, Zo-1 and Zo-2 is depend on PKC δ [33, 34].

In addition to regulating structural elements, PKCs have been implicated in modulating secretion in pancreatic ductal cells [35]. For example, substance P, which is produced in periductal nerves, activates PKC in ductal cells [36]. Active PKC then inhibits bicarbonate secretion through phosphorylation of the Cl⁻/HCO₃⁻ exchanger Solute Carrier Family 26 Member 6 (SLC26A6) [37]. SLC26A6 forms a transport metabolon when carbonic anhydrase II (CAII) binds, thereby increasing the rate of bicarbonate transfer out of the cell, as bicarbonate is then produced at the site of the transporter [37]. By phosphorylating SLC26A6 at amino-acid residue S553, PKC decreases bicarbonate secretion by blocking CAII binding [37].

3. PKC IN PANCREATIC INFLAMMATION

Pancreatic inflammation has consequences on both the endocrine and exocrine tissue, such that it contributes to diabetes mellitus as well as pancreatitis. PKC ζ , δ , and ϵ play key roles in diabetes, such that PKC ζ activation could have therapeutic benefit, while PKC δ and ϵ activity produces negative effects (Figure 3). In pancreatitis, PKCs are involved in regulating cell death pathways, generating an inflammatory response via NF- κ B activation, mediating trypsinogen activation, and redirecting exocytosis to the basolateral membrane (Figure 4).

3.1 Diabetes Mellitus

In type 2 diabetes metabolic stress induces inflammation within the pancreas that negatively affects islet function [38, 39]. Additionally, obesity, which involves chronic inflammation, induces insulin resistance in metabolic tissues [40]. When there is insulin resistance, pancreatic beta cells produce more insulin to try to lower blood glucose levels, but this usually results in exhaustion and eventually type 2 diabetes [41].

In the insulin resistant state, activation of PKC ζ seems to act protective, and the expression of constitutively-active PKC ζ in beta cells of mice results in insulin secretion as well as beta cell proliferation [42]. In addition, the knockout of PKC ζ in beta cells of mice blocks their proliferation in response to insulin resistance [43]. PKC ζ drives beta cell proliferation

through activation of mammalian target of rapamycin (mTOR) [42, 43]. Activation of mTOR then increases expression of cyclin-D2, which drives proliferation [44]. Thus, in combatting type 2 diabetes, activation of PKC ζ may have therapeutic benefit.

In contrast, PKC δ and ϵ have been shown to contribute to the development of both type 1 and type 2 diabetes. An auto-inflammatory response induces beta cell death in type 1 diabetes. In a model of this condition in which *in vitro* stimulation of islets with cytokines damaged beta cells, a knockout of PKC δ prevented apoptosis and inhibited toll-like receptor 2 (TLR2) signaling [45]. TLR2 acts as a sensor and activates antigen-presenting cells, thereby aiding type 1 diabetes development, when apoptotic beta cells are not phagocytosed but instead undergo secondary necrosis [46]. Using TLR2 knockout mice it also was shown that this receptor has a role in type 2 diabetes. A high fat diet in these mice exhibited less inflammation and greater insulin sensitivity than wildtype mice [47]. Additionally, PKC δ mediates IL-1 β -induced inflammation [48]. Activation of PKC δ via IL-1 β is essential in generating and stabilizing inducible nitric oxide synthase (iNOS) expression, which in turn generates nitric oxide (NO) that disrupts beta cell function [48, 49]. Another contributor to beta cell dysfunction, is PKC ϵ , in which knockout of PKC ϵ results in greater insulin secretion in response to glucose when islets are pretreated with fatty acids [50]. This suggests inhibition of PKC ϵ could have therapeutic benefit in type 2 diabetes, which is often modeled by fatty acid treatment that induces a reduction in beta cell mass and insulin secretion [51].

3.2 Pancreatitis

In pancreatitis, PKC isoforms δ and ϵ have been well characterized in regulating cell death pathways, generating an inflammatory response, mediating trypsinogen activation, and redirecting exocytosis to the basolateral membrane (Figure 4). For example, genetic ablation of PKC ϵ significantly attenuated necrosis and the severity of pancreatic damage in a caerulein-induced pancreatitis mouse model [52]. Furthering pancreatic injury, zymogen activation is increased and apical secretion is decreased in pancreatitis [53, 54]. One particular zymogen, trypsinogen, is activated early in pancreatitis and this induces injury [55]. Upon supraphysiological administration of CCK or caerulein, trypsinogen activation occurs in a PKC-dependent manner [20, 56]. This is mediated via both PKC δ and PKC ϵ , but not PKC α or PKC ζ , as shown with PKC $\delta^{-/-}$ mice, PKC $\epsilon^{-/-}$ mice, and specific PKC isoform inhibitors [20, 52, 56]. Additionally, when secretions occur at the basolateral membrane instead of the apical membrane, injury is induced [57]. PKC mediates a switch from apical secretion to basolateral secretion upon supraphysiological CCK administration, which experimentally induces pancreatitis [58]. By phosphorylating Munc18c, PKC α causes dissociation of Munc18c from Syntaxin-4, which leads to its proteolytic degradation in the cytosol [58–60]. Syntaxin-4 can then form a SNARE complex with SNAP-23 at the membrane and VAMP-2 on zymogen granules, thereby leading to basolateral exocytosis [58–60].

An additional role of PKC is to mediate an inflammatory response in acute pancreatitis [61], which is mediated through the transcription factor nuclear factor- κ B (NF- κ B) [55]. In CCK-induced pancreatitis models, PKC δ , ϵ , and ζ are activated, such that the translocation of

PKC δ and the activation of PKC ϵ leads to NF- κ B activation [62]. This was first shown using the PKC inhibitors GF109203X (pan-PKC inhibitor), Gö 6976 (conventional PKC inhibitor), PKC ζ pseudosubstrate (PKC ζ inhibitor), δ V1-1 (PKC δ translocation inhibitor), and ϵ V1-2 (PKC ϵ translocation inhibitor) [62]. Later, this was confirmed in isolated acinar cells of PKC $\delta^{-/-}$ mice stimulated with supraphysiological CCK [20] as well as *in vivo* in a caerulein-induced pancreatitis model where wildtype mice were treated with the PKC δ translocation inhibitor δ V1-1 [63].

4. PKC IN PANCREATIC CANCER

In pancreatic cancer, PKCs have been implicated in both tumor promoting and tumor suppressing roles. PKC isoenzymes contributing to pancreatic cancer development and progression include PKC α , PKC β , PKC δ , PKC ϵ , PKC ζ and PKC ι (Figure 5) [7, 64–66]. While PKC β , δ , ζ , ι , and to a lesser extent PKC ϵ , have been implicated in the malignancy of pancreatic cancer, the role of PKC α remains unclear, as studies have suggested opposing roles [67, 68]. In the following we will discuss the roles of these PKC isoforms in development and progression of pancreatic cancer.

4.1 PKCs in Pancreatic Cancer Development

Activating *KRAS* mutations occur in almost all pancreatic ductal adenocarcinoma (PDA) patients [69], and, being present in most acinar-to-ductal metaplasia (ADM) lesions and pancreatic intraepithelial neoplastic lesions (PanIN), are believed to be the initiating mutations leading to development of the cancer [70]. While mutant KRas has thus far not been directly targetable in pancreatic cancer [71], PKCs mediate many of the downstream effects of KRas. For example, in mice, PKC ι inhibition can mitigate Kras^{G12D}-driven formation of ADM possibly through upregulation of matrix metalloproteinase-7 (MMP-7) [72]. The likely mechanism of how PKC ι and MMP-7 regulate ADM is through Notch, since Notch can be activated by MMP-7-mediated cleavage [73] and is a driver of the ADM process [74]. However, it should be noted that it also was shown that activation of atypical PKCs causes phosphorylation of Kras^{G12V}, thereby decreasing tumorigenesis [75]. Further studies showed that PKC δ contributes to acinar cell dedifferentiation, a first step in the conversion from an acinar to a ductal phenotype [76]. This is interesting because novel PKCs such as PKC δ activate PKD1, which is necessary for oncogenic KRas-mediated ADM and PanIN formation via activation of Notch [74]. The contribution of additional PKC isoforms to pancreatic cancer development remains unclear.

4.2 PKCs in Pancreatic Cancer Progression

The PKC isoforms α , β , δ , ϵ , ζ and ι have been shown to contribute to an aggressive cancer phenotype. For example, PKC α as well as the novel PKCs PKC ϵ and PKC δ and the atypical PKCs PKC ι and PKC ζ all have been implicated in regulation of anchorage-independent growth of tumor cells. Anchorage-independent growth and cell proliferation is mediated through both the Raf-MAPK and Akt pathways. For instance, PKC α induces Raf-1 activation via phosphorylation at S499 [77] and indirect activation of Raf-1 occurs via PKC ϵ [78]. Further, conventional and atypical PKCs promote Raf-1 activation via phosphorylation of Raf Kinase Inhibitor Protein (RKIP), which subsequently releases Raf-1 thereby allowing

downstream signaling [79], and MAPK phosphorylation/activation is enhanced by PKC δ as well as PKC ϵ [65]. It was shown that in pancreatic cancer cells in response to PMA, neurotensin, and physiological levels of CCK, PKC ϵ translocates to the plasma membrane to activate the MAPK pathway and regulate proliferation [80, 81]. PKC δ has been shown to drive anchorage-independent growth through activation of the PI3K-Akt pathway, and treatment of Panc1 cells overexpressing PKC δ with the PI3K inhibitor LY294002 prevented soft agar colony formation [64]. Besides its roles in cell survival, anchorage independent growth and proliferation, PKC δ is also implicated in cell metastasis [82], and overexpression of PKC δ enhances the metastatic capability of Panc1 cells in xenografts [64].

Additional mediators of anchorage-independent growth and invasion are the atypical isoforms PKC ζ and PKC ι . In an orthotopic model where Panc1 cells with knockdown of PKC ζ were injected, tumor proliferation and metastases were significantly reduced [83]. Additionally, *in vitro* assays of anchorage-independent growth and invasion indicated that PKC ζ mediates these processes through STAT3 activation, but not ERK1/2 signaling [83]. This is not surprising, as STAT3 activity has been implicated in similar processes as PKC ζ , such that constant STAT3 activity promotes PanIN and pancreatic cancer progression in a Kras^{G12D} model [84]. Further PKC involvement in PDA progression comes from PKC ι , which is associated with reduced survival in patients with high PKC ι expression [66, 85]. *In vitro*, PKC ι regulates anchorage-independent growth; and *in vivo* an orthotopic model using Panc1 cells with knockdown of PKC ι results in decreased proliferation, metastases, and angiogenesis. PKC ι knockdown also decreased the abundance of Rac1 and vascular endothelial growth factor (VEGF) expression and ERK1/2 phosphorylation [66]. However, in contrast to this, the atypical PKC activator prostratin prevents tumor progression in mice [86].

In addition to regulating tumor growth and progression, PKCs also can mediate resistance to treatment. For example, chemoresistance is caused by TGF- β 1-induced PKC α upregulation in BxPC3 cells [87]. In addition, PKC α also mediates TGF- β -induced EMT and knockdown or inhibition of PKC α suppresses Snail and blocks PTEN downregulation [88, 89]. Another conventional PKC, PKC β , has been implicated as integral in angiogenesis and radioresistance of tumor cells. In a mouse xenograft model the PKC β inhibitor LY333531 suppressed angiogenesis and induced apoptosis [90]. In an additional study, the PKC β inhibitor enzastaurin failed to prevent overall tumor growth, but caused a delay in tumor growth when cells were irradiated [91]. In pancreatic cancer cells, resistance to radiotherapy is mediated by glycogen synthase kinase 3 β (GSK3 β), since expression of a kinase-dead version of this kinase results in radioresistance and expression of a constitutively-active version in radiosensitization of cells [92]. The mechanism of how PKC β reduces radiation cytotoxicity occurs through mediating an inactivating phosphorylation of GSK3 β at amino acid residue S9 [91, 93, 94].

Another PKC that is activated by irradiation is PKC δ . Ionizing radiation causes cleavage and activation of caspases 3 and 7, of which caspase 3 cleaves PKC δ , resulting in an active, unregulated kinase fragment [95, 96]. This active PKC δ fragment then activates Akt to drive tumor cell proliferation [82]. While PKC ϵ can be activated by caspase 3 by a similar mechanism, it so far has not been implicated in this pathway [96].

Taken together, PKCs have been implicated in almost all aspects of pancreatic cancer progression, including angiogenesis, anchorage-independent growth, radioresistance and metastasis, suggesting inhibition could have a positive therapeutic role.

4.3. Targeting PKC in pancreatic cancer

Most work in pancreatic cell lines and mouse models have shown activation of PKCs to increase malignancy. Therefore, therapeutic approaches have focused on inhibiting PKCs. However many PKC mutations in cancer are loss-of-function mutations [97]. For example, the PKC γ mutation P524R prevents activation in response to stimuli and this residue in an analogous position in PKC δ , ϵ , and θ is also mutated such that it loses function in pancreatic cancer [97]. Additionally, many PKC inhibitors have not been successful in the clinic (for a review of PKC therapeutic strategies, see [98]). For example, bryostatin-1, which initially activates PKC but then downregulates it upon further exposure [99], was an initial promising target as shown by its efficacy in increasing apoptosis following gemcitabine treatment of human pancreatic cancer cell lines [100]. However, in a phase II clinical trial where bryostatin-1 was used in conjunction with paclitaxel in advanced stage pancreatic adenocarcinoma patients, bryostatin-1 was not effective in improving patient survival or decreasing tumor burden [101].

In contrast, PKC α , β I, and δ show increased expression in pancreatic cancer tissue versus normal tissue, suggesting inhibition of these isoforms has therapeutic potential [100]. For example, the orthotopic injection of HPAC cells overexpressing PKC α increased the mortality rate in mice, while down-regulating PKC α expression increased survival [102]. This suggests that inhibition of PKC α may be beneficial to patients. However, it should be noted that PKC α also has been shown to inhibit pancreatic cancer cell proliferation in cell lines [67] and induce increased expression of Bad as well as the TRAIL receptors DL4 and DL5, thereby making cells sensitive to apoptosis [68]. Taken together, the often contradictory results obtained by using animal models, cell lines or inhibitors clearly indicate that more studies are needed to understand the roles of PKC isoforms in the development and progression of this cancer, before meaningful therapeutic targeting strategies can be developed.

5. CONCLUSION

PKCs regulate many pancreatic functions in normal acinar cells, ductal cells, and islets, as well as in disease states, including insulin resistance, diabetes mellitus, pancreatitis and pancreatic ductal adenocarcinoma (PDA). In the normal pancreas PKCs regulate secretory mechanisms, as seen by amylase secretion in acinar cells, bicarbonate secretion in ductal cells, and glucagon as well as insulin secretion in islets. PKCs are also essential in insulin resistance and diabetes mellitus development where they regulate β -cell proliferation and function as well as insulin secretion and β -cell destruction. During pancreatitis, PKCs are key players contributing to pancreatic damage and inflammation, as well as trypsinogen activation and basolateral exocytosis. Eventually PKCs also contribute to PDA development by contributing to acinar cell dedifferentiation (PKC δ) [76] and acinar-to-ductal metaplasia (PKC λ) [72]. During the progression of PDA, PKC α , PKC δ , PKC ϵ and the atypical PKCs

PKC ζ and PKC ι regulate proliferation and enhance anchorage-independent growth [65, 66, 77–79, 83]. In addition, atypical PKCs also have been implicated in regulating metastasis [66, 83]. In summary, PKC isoforms have diverse roles in maintaining normal pancreatic function, but they can also contribute to the induction and progression of pancreatic disease.

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ABBREVIATIONS

ADM	acinar-to-ductal metaplasia
BIM	bisindolylmaleimide
CCK	cholecystokinin
DAG	diacylglycerol
DRM	detergent-resistant membrane fraction
EX4	exendin-4
GLP-1	glucagon-like peptide-1
GSK3β	glycogen synthase kinase 3 β
iNOS	inducible nitric oxide synthase
KEAP1	Kelch-like ECH-associated protein 1
MANS	myristoylated N-terminal sequence of MARCKS
MARCKS	myristoylated alanine-rich C kinase substrate
MMP-7	matrix metalloproteinase-7
NF-κB	transcription factor nuclear factor- κ B
NO	nitric oxide
PKC	protein kinase C
PLC	phospholipase c
RKIP	Raf Kinase Inhibitor Protein
SLC26A6	Solute Carrier Family 26 Member 6
TLR2	toll-like receptor 2
TPA	12- <i>O</i> -Tetradecanoylphorbol-13-acetate

VEGF vascular endothelial growth factor

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Highlights

- PKCs play key roles in acinar, ductal, and islet cells of the pancreas.
- PKCs are involved in pancreatic inflammation, contributing to insulin resistance, diabetes mellitus, and pancreatitis.
- PKCs mediate pancreatic cancer development and progression.

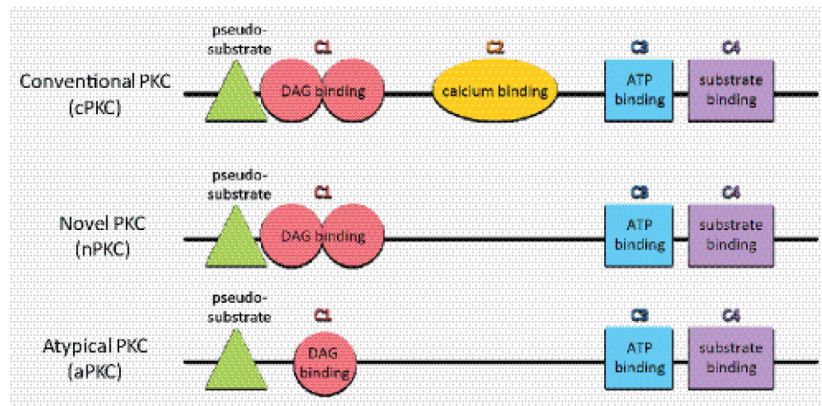


Figure 1.

PKC structure is similar across family members, although they have different activation requirements. The inhibitory pseudosubstrate domain and the kinase domain, consisting of C3 and C4, are similar amongst PKCs, but the regulatory domains differ. Conventional PKCs (cPKCs) require DAG and calcium binding, while novel PKCs (nPKCs) require DAG binding, and atypical PKCs (aPKCs) require neither DAG nor calcium binding, although they have a single Cys-rich motif (C1).

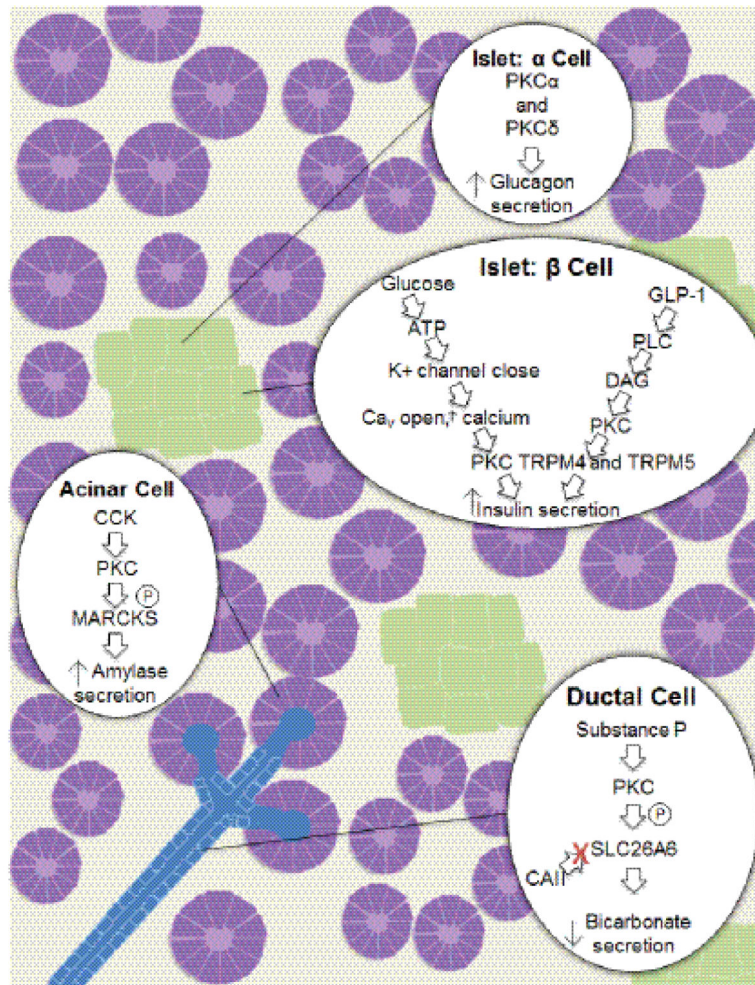


Figure 2. PKC functions in the normal pancreas. PKCs regulate hormone secretion in the islets, amylase secretion in acinar cells, and bicarbonate secretion in ductal cells of normal pancreatic tissue. In islets, PKC α and PKC δ regulate Glucagon secretion from alpha-cells. In addition PKCs regulate insulin secretion in beta-cells. Amylase secretion is increased in acinar cells after stimulation of the CCK receptor and bicarbonate secretion is downregulated in ductal cells after activation of PKC via Substance P.

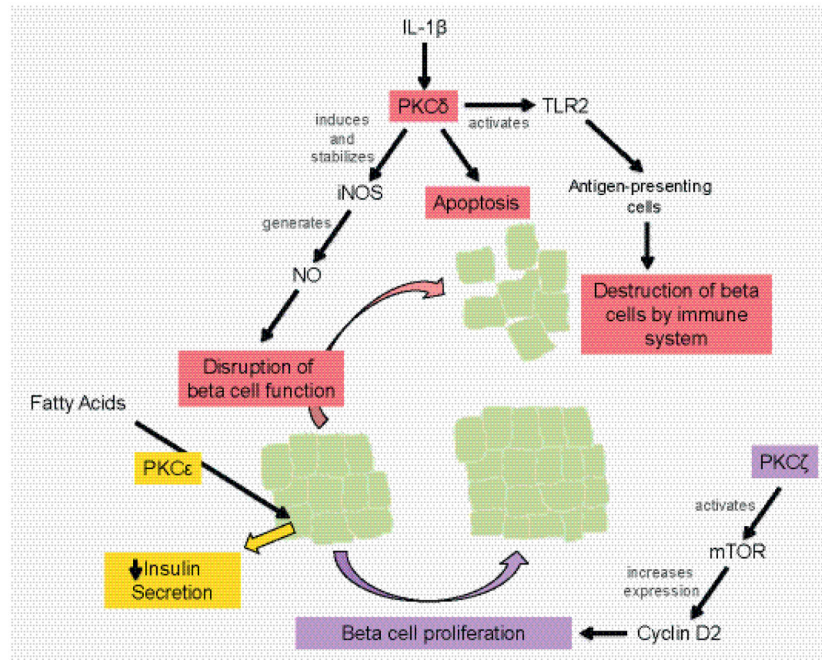


Figure 3.

Roles of PKC isoforms in islet function. In diabetes mellitus development, PKC ζ activity promotes beta cell proliferation through mTOR activation, while PKC δ promotes dysfunction and destruction of beta cells via iNOS expression and TLR2 signaling. In a type two diabetes model where islets are pre-treated with fatty acids, PKC ϵ is integral to the resulting decrease in insulin secretion.

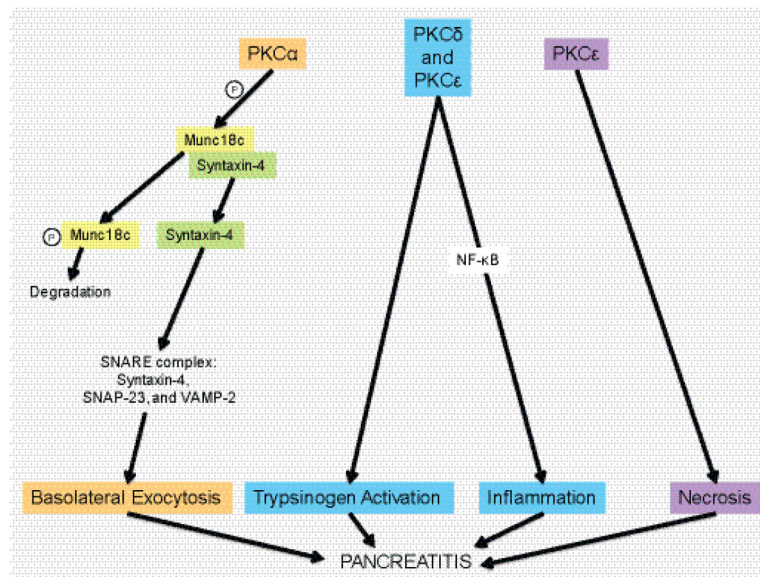


Figure 4. Schematic of how PKD isoforms contribute to pancreatic inflammation (pancreatitis). PKC α can aid basolateral exocytosis via phosphorylation of Munc18c. This leads to Munc18c degradation and release of Syntaxin-4 and formation of the SNARE complex. PKC ϵ has been implicated in necrosis linked to pancreatitis and both, PKC δ , and PKC ϵ also contribute to trypsinogen activation and activation of NF- κ B, which drives inflammation.

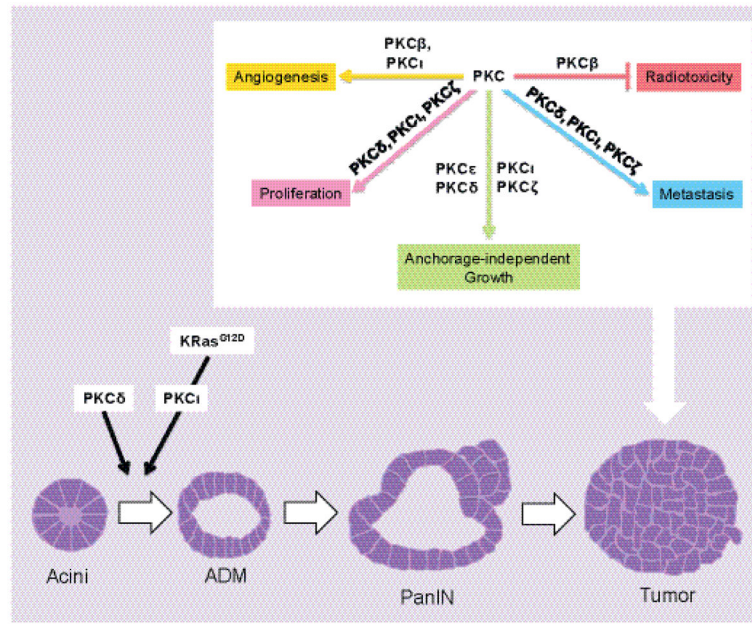


Figure 5.

Schematic of a progression model for pancreatic cancer. Current belief is that acinar cells (acini) can undergo acinar-to-ductal metaplasia (ADM). In presence of an oncogenic *KRAS* mutation, ADM lesions further develop into pancreatic intraepithelial neoplasia (PanIN), which then can progress to pancreatic cancer. PKC δ and PKC ι contribute to the early event of ADM and additional PKCs mediate the growth and progression of pancreatic cancer by aiding angiogenesis, proliferation, anchorage-independent growth, and metastasis, while also preventing radiosensitization.