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The many hats of delta protein kinase C; one enzyme with many functions

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Introduction

Protein kinase C delta (PKC δ) has been cloned over 25 years ago [1] and many studies have identified diverse roles and substrates for this member of the family of PKC enzymes in normal and in pathological conditions. Although PKC δ has been implicated in diverse human diseases, including cancer [2], stroke [3], ischemic heart disease [4, 5], diabetes [6, 7], neurodegenerative diseases [8, 9], sepsis [10], *etc.*, there are no approved drugs affecting this isozyme. In this brief review, we will discuss some of the challenges in drug development that will regulate the multi-functional, PKC δ .

Technical Approaches to Identifying The Role of PKC δ

Over the years, a variety of tools were used to determine the role of PKC δ in normal and disease states. They include pharmacological and genetic tools and they are described briefly in the following.

1. Competitive inhibitors of the catalytic site or the regulatory site of the enzyme

PKC δ is a member of the highly homologous, diacylglycerol-dependent Ser and Thr protein kinase C family (PKC) (Fig. 1). Because the catalytic domain of PKC is highly similar to many of the other protein kinases, in contrast to early reports, most of the competitive inhibitors of the ATP-binding site were found to be non-selective [11]. A common compound that was used to study the role of PKC δ is rottlerin [12]. However, rottlerin is a potent large conductance potassium channel opener, and it affects multiple other protein kinases [13]. Due to their non-selective nature, competitive inhibitors of the catalytic site are not optimal as tools to identify the role of PKC δ .

Another target for PKC regulators is focused on the regulatory domain of the enzyme. Initial studies used phorbol esters that bind to the diacylglycerol-binding site in the C1 domain

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NQ and DMR have no current conflict to report.

(Fig. 1), at high (nM) affinity [14]. However, phorbol esters activate all the classical and novel PKC isozymes (Fig. 1) as well as some other non-PKC C1-containing proteins [15]. Another approach focused on generating isozyme-selective synthetic analogs of bryostatin, a family of natural products from the marine bryozoan, *Bugula neritina*; one analog improved selectivity for PKC δ [16]. However, activation by bryostatin is much longer lasting and subcellular localization of the activated isozyme may be different than when activated with diacylglycerol or other endogenous stimuli [17]. Therefore, in general, it has proven difficult to selectively activate PKC δ by focusing on the diacylglycerol site [18].

2. Genetic tools

Some of the data regarding the role of PKC δ were generated using genetic tools in which the enzyme was knocked out or over-expressed. However, conflicting data were obtained, even in the same or similar systems. For example, in one study, mice over-expressing PKC δ in basal epidermal keratinocytes exhibited attenuated progression of papilloma to squamous cell carcinoma (SCC) [19]. In contrast, another study showed that over-expression of PKC δ in human SCC lines and in mouse epidermis induced apoptosis and suppressed tumorigenicity, suggesting that PKC δ activation selectively inhibits SCC [20]. Notably, PKC $\delta^{-/-}$ mice develop normally, and only under specific conditions exhibit a phenotype different from wild type, PKC $\delta^{+/+}$ mice. For example, PKC $\delta^{-/-}$ have increased arteriosclerotic lesions in vein grafts as compared to wild-type mice [21] and PKC $\delta^{-/-}$ smooth muscle cells are resistant to apoptosis by a variety of stimuli (UV, TNF- α , IL-1 β , IFN- γ , and H₂O₂; [21]). Further, under ischemic conditions, the levels of enzymes related to energy and metabolism are altered in PKC $\delta^{-/-}$ leading to a shift from glucose to lipid metabolism in the hearts of PKC $\delta^{-/-}$ mice [22]. Therefore, the lack of severe phenotype in PKC δ null mice likely reflects compensation for the loss of this enzyme by other protein kinases, limiting the ability to assess the role of this enzyme in human diseases using genetic tools.

3. PKC δ -selective regulators of protein-protein interactions

In 1991, we described the rational design and the application of an isozyme-selective inhibitor and an isozyme-selective activator of PKC δ [4]. These PKC δ -selective regulators are short peptides, derived from PKC δ ; they inhibit or induce the activation and translocation of this isozyme, by selectively competing with PKC δ -selective protein-protein interactions (PPIs). The peptide inhibitor, δ V1-1, inhibits a PPI between PKC δ and its anchoring protein, RACK δ . The peptide activator, ψ δ RACK, inhibits intramolecular PPI, which keeps PKC δ in the inactive form, thus leading to selective activation of PKC δ (Fig. 2; [23, 24]). δ V1-1 corresponds to amino acids 8–17 in the C2 domain of PKC δ whereas ψ δ RACK corresponds to amino acids 74–81 in the C2 domain of PKC δ [4]; these sequences are unique to PKC δ , are conserved in evolution and are absent in the other PKC isozymes.

Although peptides are not cell permeable, cross-linking them to HIV TAT protein-derived cell permeable peptide, TAT_{47–57}, enables the delivery of these peptides into cells when used in cells in culture as well as *in vivo* [25]. Effective delivery is observed following intraperitoneal injection (for acute treatment) or subcutaneous delivery, using an Alzet pump, for sustained delivery (*e.g.* [3] and [9], respectively). The peptides are well tolerated at

doses greater than 3 mg/Kg/day, even when delivered for many weeks, and can access all tissues, including across the blood-brain barrier [9].

Many PKC δ functions have been identified using these peptide regulators in our laboratory as well as in other laboratories. Here we focus on some of the PKC δ functions that were identified in our laboratory.

In the first study with these short peptide regulators, we showed that PKC δ increases damage induced by cardiac ischemia (heart attack) *in vitro* and *in vivo* [4]. These studies in rats and mice were subsequently confirmed also in a porcine model of heart attack [5]; both acute 70% reduction in infarct size and a sustained improvement in cardiac functions were observed. A statistically significant benefit was also observed in a small human study of patients with myocardial infarction when the peptide inhibitor, δ V1-1, was delivered at reperfusion and directly through the previously occluded coronary artery, as in the porcine model [26]. We then showed that injury induced by PKC δ activation during reperfusion is not selective to cardiac myocytes. PKC δ activation in the microvasculature impairs blood flow in the infarcted tissue after opening the occluded artery due to induced swelling and apoptosis of the endothelial cells in the microvasculature [27]. Finally, one of the major benefits of PKC δ inhibition during reperfusion injury following myocardial infarction was found to be the increase in ATP regeneration; whereas in control-treated hearts ATP levels remained at 20% of basal, 30 minutes after treatment with δ V1-1, ATP levels were at 70% of basal [5]. Therefore, an inhibitor of PKC δ reduces the overall damage to the myocardium and tissue necrosis following myocardial infarction by increasing ATP regeneration as well as keeping the microvascular patent during the reperfusion period.

In other studies, activation of PKC δ in skeletal muscle cells was found necessary for cell spreading in a mechanism mediated by the phosphorylation of MARCKS, and the reorganization of the actin cytoskeleton [28]. Selective activation of PKC δ with ψ δ RACK promoted attachment of these muscle cells to fibronectin, suggesting a role for this isozyme in muscle response to injury [28]. We also found that a brief treatment with the PKC δ inhibitor, δ V1-1, prevents accelerated coronary artery disease in transplanted hearts *in vivo* in a murine cardiac allograft transplantation model [29]; cardiomyocyte apoptosis and caspase-3 and caspase-9 (but not caspase-8) activities were significantly reduced following δ V1-1 treatment. PKC δ activity also inhibits proliferation of rat cardiac fibroblasts [30]; treatment with δ V1-1 increased basal proliferation, but did not affect TGF β 1-induced cell proliferation, suggesting a role for this isozyme in tissue repair following injury. Together, these and other studies indicate potential use of PKC δ -selective agonists and antagonists as treatments for a variety of human diseases, including myocardial infarction, heart transplantation and the development of heart failure [31].

Other Challenges in Generating Regulators of PKC δ

1. PKC δ is activated by a variety of mechanisms

A challenge in assessing the functions of PKC δ is that in addition to its activation by the lipid-derived diacylglycerol [32], the function of PKC δ has been shown to be regulated by proteolysis, tyrosine phosphorylation, intracellular localization, oxidation and other protein

modifications (reviewed in [33]; [34]). Further, PKC δ activation can be affected by cell type, the form and extent of different PKC δ protein modifications, as well as by co-stimulation with other signaling events [33]. It is likely that the different forms of activated PKC δ will not be equally sensitive to pharmacological agents targeting this enzyme. For example, PKC δ inhibitors or activators that bind to the regulatory domain of the enzyme will not affect the catalytic fragment of PKC δ , often found in cancer. Likewise, protein modifications may alter the interaction of the pharmacological agent with PKC δ . Therefore, it may be necessary to screen for PKC δ regulators using the enzyme in the specific state of modification (*e.g.* Tyr phosphorylation or oxidation) that is specific for the target pathology (*e.g.* cancer *vs.* ischemic injury in the heart).

2. PKC δ has multiple protein substrates

The use of the PKC δ -specific inhibitor and activator enabled the identification of PKC δ -specific substrates. PKC δ substrates were identified in a variety of subcellular sites, including the cytosolic M2 pyruvate kinase [35], the cytoskeletal proteins, MARCKS [28] and troponin [36], the nuclear protein, DNA-dependent protein kinase (DNA-PK) [37], the mitochondrial surface proteins, dynamin-related protein 1 [8] and BAD [38], and the mitochondrial matrix enzyme, pyruvate dehydrogenase reactivation [39].

By phosphorylating such diverse substrates at different subcellular locations, PKC δ was shown to be directly involved in diverse responses even within the same cell type subjected to the same stimulus. For example, we found that after myocardial infarction, activated PKC δ triggers cardiac myocyte apoptosis, possibly by affecting BAD phosphorylation (directly or indirectly) [38]. As discussed above, we also found that PKC δ activation leads to necrosis by inhibiting ATP regeneration; this occurs by direct phosphorylation and activation of pyruvate dehydrogenase kinase (PDK) [39]. Activated pyruvate dehydrogenase kinase, in turn, phosphorylates and inactivates pyruvate dehydrogenases, thus shutting off the Krebs cycle [39]. (Direct phosphorylation of PDK was observed *in vitro* and in hearts subjected to ischemia and reperfusion and δ V1-1 inhibited this phosphorylation [39]). PKC δ activation also triggers endoplasmic reticulum stress-induced response and apoptosis [40, 41] in a mechanism that is dependent on tyrosine phosphorylation of PKC δ and its physical association with c-Abl. However, what substrates are phosphorylated by activated PKC δ in the endoplasmic reticulum and how this phosphorylation results in endoplasmic reticulum-dependent apoptosis is not known. We also found that PKC δ activation following ischemia and reperfusion induces excessive mitochondrial fission, fragmentation and dysfunction by phosphorylating and activation of the pro-mitochondrial fission protein, dynamin-related protein 1 (Drp1) by phosphorylating Ser579 in the protein [8]. Selective inhibition of Drp1 activation (using P110, a novel inhibitor of Drp1 that we designed) reduces infarct size and prevents development of heart failure following myocardial infarction [42]. These data suggest a central role for PKC δ -mediated and Drp1-dependent excessive mitochondrial fragmentation in cardiac ischemic injury. Finally, we found that PKC δ activation inhibits removal of damaged mitochondria (mitophagy) by lysosomal-like structures following ischemia-induced injury; this effect is mediated by a direct phosphorylation of mitochondria-associated glyceraldehyde-3-phosphate dehydrogenase (GAPDH) on Thr246 residue by PKC δ [43]. We also showed that expression

of a GAPDH Thr246Ala mutant promoted mitochondrial uptake increased mitophagy and reduced apoptosis following ischemia. How critical is PKC δ -mediated inhibition of mitophagy to cardiac infarction has not yet been determined, as a selective inhibitor of mitophagy has not yet been identified.

Open Questions

Do all these PKC δ -mediated phosphorylations contribute equally to cardiac infarction? Therefore, would inhibition of all of these phosphorylations in non-ischemic tissue be safe? Clearly, inhibition of phosphorylation of some of these substrates is cardioprotective; *e.g.* inhibiting the phosphorylation of the mitochondrial pyruvate dehydrogenase kinase by PKC δ directly increases ATP regeneration and thus the repair capacity of the myocardium [5]. However, it is possible that phosphorylation of some of the PKC δ substrates is essential for normal cellular functions and that inhibition of the phosphorylation of these substrates will result in worse cardiac damage.

Taken together, it is possible that an inhibitor of the phosphorylation of all the protein substrates of PKC δ is less desired than inhibitors of a subset of phosphorylation events. Our current research focuses on generating such inhibitors, which we termed separation of function inhibitors or SoFIs. Whether such inhibitors can be identified and whether they will provide better therapeutic effects remains to be determined.

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Figure 1. PKC δ is a member of the family of highly homologous PKC isozymes. A scheme identifying the common, highly homologous regions C1, C2, C3 and C4, and the short intervening less homologous regions, V1, V2, V3, V4 and V5.

Figure 2.

A scheme describing PPIs as targets for selective regulators of PKC δ . Left: A scheme of a PPI peptide inhibitor of PKC δ interaction with its anchoring molecule, RACK. The peptide that corresponds to the RACK-binding site in the enzyme, competes with association of the activated PKC δ close to its substrate, thus leading to a loss of the physiological responses of PKC δ . Right: A scheme of a PPI peptide activator of PKC δ . The peptide, derived from a site on PKC δ that mimics the PKC δ -binding site on its RACK, is thus called pseudo-RACK site or ψ RACK site. A peptide corresponding to ψ RACK site competes with the intramolecular inhibitory PPI within PKC δ , leading to its activation. As the affinity of the RACK for PKC δ is greater, the peptide is replaced by the RACK, which brings the activated PKC δ near its substrate. Phosphorylation of that substrate leads to physiological responses. Many studies demonstrated the selectivity of these peptides for the given isozyme. Also reviewed in [23, 24, 31].