PKCδ: A Protein of Many Functions

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Abstract
Protein Kinase C delta (PKCδ) is a newly characterized member of the PKC family, a group of 11 isozymes classified as serine/threonine protein kinases. This family plays a critical role in regulating several signal transduction pathways. The general structure is divided in three regions: a catalytic domain, regulatory domain, and N terminus. PKCδ is comprised of nine isoforms observed in human (I/VIII), rat (I/III) and mouse (I/III/IV-VII/IX). Function differs with cellular location and includes promoting cell survival, growth and development, tumor suppression and apoptosis. Alternative expression of the PKCδ isoforms has been demonstrated to regulate cellular differentiation during neurogenesis (PKCδII) and initiation of apoptosis (PKCδI). Unlike conventional PKCs, PKCδ is activated by diacylglycerol and phospholipid in a Ca²⁺-independent manner. The regulatory domain of PKCδ includes C1 and C2-like motifs separated by a hinge region (V3), which regulates protein activation. This model emphasizes the C2-like domain of PKCδ, which targets the protein for expression at the membrane. Three unique tryrosine residues are significant for function: Tyr12 replaces a highly conserved alanine or glycine and is involved in stabilizing a hydrophobic core of the protein; Tyr52 is an essential phosphopeptide regulatory site; and Tyr64 regulates nuclear localization of the protein and induction of apoptosis. Residues essential for docking binding partners to this signaling protein include Thr58, a potential essential phosphopeptide regulatory site; and Tyr64 regulates nuclear translocation of the protein;2 Tyr52 is essential for binding to signaling partners.4

Introduction
PKCδ is not your typical PKC isoform (Figure 1). The PKC family consists of three different classes; the classical group α, β, and γ, the atypical group, η and ξ, and lastly, the novel group, δ, ε, and θ (Figure 2). The novel class has many unique features. PKCδ is calcium independent, has a phosphopeptide binding site and a dual effect on cellular activities. The C2-like domain is regulated by phosphorylation, and activated by diacylglycerol and phorbol ester. In addition, the C2-like domain is a selective inhibitor of translocation and function of the corresponding isozymes; PKCδI and PKCδII. PKCδ isoforms were explored in studies of retinoic acid induced differentiation of human NT2 cells. Although PKCδI and II have similar structures, they perform different functions; PKCδII promotes apoptosis while PKCδII promotes cell survival (Figure 3).2

Figure 1: Model of PKCδ C2-like domain. Based on 8YD1.pdb.9

Figure 2: A schematic diagram of the PKC protein family; classical (c), novel (n), and atypical (a).2

Figure 3: A diagram of the polarizing roles of PKCδ activity in survival and apoptosis. Depending upon caspase 3 cleavage of the V3 region of the protein, PKCδ can be involved in either pathway.7

Figure 4: Mouse embryonic stem cells differentiate into dopaminergic neurons with retinoic acid (RA) and ciliary neurotrophic factor (CNTF) treatment. A. mRNA expression of PKCδI vs. PKCδII in developing neurons. B. Mouse embryonic stem cell (mES) growth after 2 weeks. C. mES growth after stimulation with RA and CNTF.1

What’s the Next Question?
Although the structure of the C2-like domain of the molecule of PKCδ is analogous to the C2 domains of most proteins, the uniqueness of the binding surfaces found on the C2-like domain raise several questions that are now being investigated. When PKCδ is activated by the immunoglobulin E receptor, Tyr52 is phosphorylated by the Src protein Lyn and serves as a docking site for the SH2 (Src homology 2) domain of Lyn. The SH2 domain of Lyn acts as a docking site for other proteins including SHIP-1.10 PKCδ may play a role in the regulation of these proteins and these relationships should be further investigated.

Summary
Unlike typical PKCs, the C2-like domain of PKCδ is Ca²⁺-independent and is an important site for DAG and phospholipid binding. This novel regulation strategy permits unique and diverse functions to be regulated by PKCδ. The opposing functions of PKCδ isoforms suggest various functions that this molecule can take in promoting a better solution to multiple cancers, Alzheimer’s disease, and even Parkinson’s disease.

How Do We Know?
Mouse embryonic stem cells (mES) differentiate into neuronal cells after stimulation with RA and CNTF. This differentiation is accompanied by increased PKCδII mRNA expression, which suggests a role of PKCδII in neurogenesis. Addition of brain derived neurotrophic factor (BDNF) and epidermal growth factor (EGF) did not increase PKCδII mRNA expression (Figure 4).1

ParC5 (parotid acinar cells) were transfected with three plasmids, pWT6, p52F6, and p64F6 (Figure 5). Eighteen hours after transfection, cells were left untreated (Cont), treated with etoposide (Etop), or phorbol 12-myristate 13-acetate (PMA). Addition of a negative charge by aspartic acid, which mimics phosphorylation at T64, is sufficient to target the protein for translocation to the nucleus, thereby regulating apoptosis by controlling nuclear translocation of PKCδ.6

References
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