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Protein Kinase D: A Potential Therapeutic Target in Prostate Cancer

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Abstract

Protein kinase D (PKD) belongs to a family of serine/threonine kinases in the calcium/calmodulin-dependent kinase superfamily. It modulates a number of signal transduction pathways involved in regulation of cell proliferation, survival, migration, angiogenesis, regulation of gene expression, and protein/membrane trafficking, mediated by variety of stimuli such as growth factors, hormones, and cellular stresses. Although its role in cancer progression remains elusive, current literature supports a potential tumor promoting function of the selective PKD isoforms in prostate cancer, making them promising therapeutic targets for cancer treatment.

Keywords

Protein kinase D; Prostate cancer; Therapeutic target; Signal transduction

Introduction

The protein kinase D (PKD) family of serine/threonine kinases belongs to the Ca^{++} /calmodulin-dependent protein kinases (CaMKs) superfamily and consists of three isoforms in mammals, notably, PKD1, PKD2 and PKD3 (1). PKDs are evolutionarily highly conserved and homologs are found in several organisms including yeast, mice, rats and flies. The PKD isoforms show high sequence homology and wide tissues distributions. Different stimuli such as hormones and growth factors activate PKDs via a canonical pathway involving activation of phospholipase C (PLC), generation of diacylglycerol (DAG), and downstream activation of classical/novel protein kinase Cs (c/nPKCs), which directly phosphorylates PKD on two conserved serine residues in its activation loop, leading to its activation (2). Activated-PKD regulates many cellular functions, especially those related to malignant transformation such as cell proliferation, migration/invasion, epithelial-to-mesenchymal transition (EMT), and angiogenesis (1) (Fig. 1B).

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Conflicts of Interest

No conflicts of interest to declare.

Structural-functional properties and regulation of cancer-associated signaling pathways

PKD isoforms share several conserved structural motifs including two cysteine-rich zinc finger-like C1 domains (C1a and C1b) and a pleckstrin homology (PH) domain in the regulatory region (Fig. 1A). The C1 domains bind to DAG and phorbol esters and anchor PKD to membranes and play an important role in spatio-temporal regulation of PKD localization at different subcellular locations such as Golgi apparatus and nucleus. PKD is activated by various stimuli such as chemokines, tumor necrosis factor (TNF), lipids and growth factors via the canonical pathway (3). It can be activated in various subcellular organelles such as Golgi, nucleus and mitochondria, where it phosphorylates a variety of substrates such as class II HDACs, CREB, CERT and SSH1L via a unique substrate recognition motif (L.X.R. (Q/K/E/M).S.X.X.X.X) (4), and modulates a wide range of biological processes (3,5) (Fig. 1B).

As a signaling protein, PKD modulates several important cancer-associated signaling pathways. Both positive and negative roles of PKD have been implicated as follows: (i) When activated by mitogenic GPCR agonists, PKD causes persistent extracellular-regulated protein kinase (ERK) activation, leading to cell cycle progression and cell proliferation (6,7). (ii) PKD promotes cell survival during oxidative stress by activating IKK α -IKK β -NEMO complex and nuclear import of NF κ B resulting in induction of prosurvival genes and antioxidant enzymes (8-10). (iii) PKD also regulates EMT by modulating functions of key EMT target proteins such as E-cadherin, Snail. (iv) PKD regulates cell migration and invasion by modulating several key proteins involved in actin cytoskeleton remodeling and degradation of extracellular matrix such as cofilin, SSH1L, matrix metalloproteases (MMPs) (11-14). (v) PKD has been reported to be major modulator of angiogenesis by phosphorylating class IIa HDACs, sequestering them to cytosol by 14-3-3 adaptor proteins leading to derepression of VEGF-responsive genes (15,16).

PKD as a promising therapeutic target in prostate cancer

As one of the most common male malignancies, prostate cancer (PrCa) accounts for 13% cancer-related deaths in the USA in 2016. High mortality in PrCa associates with late stage metastatic castration-resistant prostate cancer where effective treatments are scarce. Aberrant expression and activity of PKD have been demonstrated in PrCa (17,18). Studies at cellular levels have demonstrated important functional link of PKD to PrCa cell biologies, and isoform-selective functions have been noted. With regard to PKD1, both pro- and anti-cancer activities have been demonstrated. It has been shown to negatively regulate PrCa cell proliferation and migration/invasion (19,20), suggesting a tumor suppressive role of this isoform in PrCa. However, tumor promoting effects of PKD1 have also been demonstrated in several studies. For example, it has been shown that PKD1 negatively regulates the function of androgen receptor (AR) and thus, makes the tumor resistant to hormone therapy (21). It has also been reported that PKD1 induces the expression of MMP1 and hence promotes cell migration and invasion via Wnt5a-JNK signaling axis (22). We have shown that upregulation of PKD1 as a result of loss or inhibition of AR may

contribute to the promotion of PrCa cell survival (23,24). In contrast, with regard to PKD2 and PKD3, considerable evidence supports a general tumor promoting role of these isoforms in PrCa. Elevated expression of these PKDs promotes cell survival, migration/invasion, and therapy resistance. PKD2 increases MMP-9 expression (25), inhibits apoptosis by activating ERK-1/2 and NF κ B signaling pathways (24) and thus, contributes to PrCa progression. Elevated PKD3 prolonged activation of Akt and ERK-1/2 (18,25), and induced PrCa cell migration and invasion by positively regulating NF κ B signaling and HDAC1-mediated urokinase type plasminogen activator (uPA) expression (26). In line with these findings, several PKD small molecule inhibitors such as CID755673 and its analogs kb-NB142-70 as well as CRT0066101, SD-208, 1-naphthyl PP1 (1-NA-PP1) and Compound 139 (25,27-30) consistently blocked cell proliferation and inhibited migration and invasion of PrCa cells (Fig. 1C), validating PKD as a promising therapeutic target in PrCa.

Concluding remarks

Growing evidence has demonstrated aberrant expression and activity of PKD in tumor tissues and important roles in oncogenic pathways in major human cancers including prostate cancer (5). PKD inhibitors have consistently displayed potent anticancer activities in various cancer models both *in vitro* and *in vivo*. These studies identify PKD as a potential therapeutic target for prostate cancer and justify the development of PKD-targeted small molecules for cancer therapy.

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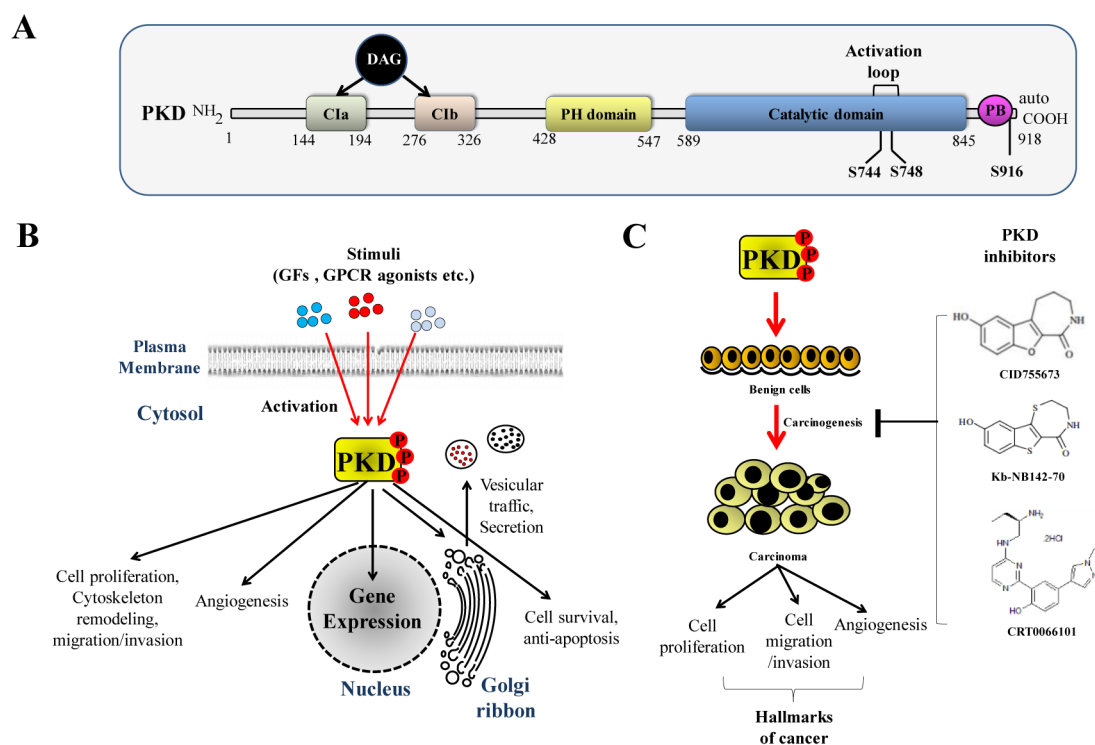


Figure 1. Role of PKD in cancer.

(A) Schematic representation of PKD structure. PKD regulatory domain contains two cystein-rich zinc finger-like motifs (C1a and C1b), a pleckstrin homology (PH) domain and C-terminal catalytic domain. The activation loop contains the two conserved serine residues and phosphorylation of which leads to PKD activation. The phosphorylation sites are numbered based on murine PKD1. (B) Major cancer-related signaling pathways regulated by PKD. (C) Illustration of some major PKD inhibitors and their inhibitory role in cancer progression.