Emerging Roles of Protein Kinase D1 in Cancer

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Abstract

Protein Kinase D1 (PKD1) is a serine-threonine kinase that regulates various functions within the cell including cell proliferation, apoptosis, adhesion, and cell motility. In normal cells, this protein plays key roles in multiple signaling pathways by relaying information from the extracellular environment and/or upstream kinases and converting them into a regulated intracellular response. The aberrant expression of PKD1 is associated with enhanced cancer phenotypes such as deregulated cell proliferation, survival, motility and epithelial mesenchymal transition (EMT). In this review, we summarize the structural and functional aspects of PKD1 and highlight the pathobiological roles of this kinase in cancer.
**Introduction**

Protein kinase D1 (PKD1) is a ubiquitous serine-threonine protein kinase that is involved in a multitude of functions in both normal and diseased states (1-3). This evolutionarily well conserved protein, with homologues in mice (*M. musculus*), rats (*R. norvegicus*), flies (*D. melanogaster*), worms (*C. elegans*) and yeast (*S. cerevisiae*), was initially recognized as a member of the protein kinase C (PKC) family and was named PKC\(\mu\) (2, 3). However, distinct differences in the protein structure, variation in substrate(s) and inhibitor specificity, and low homology of the kinase domain to other members of the PKC family resulted in its reclassification. PKD1 is now classified as a member of the protein kinase D (PKD) family, a distinct branch under the calcium/calmodulin dependent protein kinase (CaMK) branch of the cellular kinome (4). The PKD family possesses substrate specificity and characteristics that combine the structural features of the PKC and CaMK protein kinase families, uniquely positioning it to perform key functions in multiple signaling pathways. PKD serves to integrate signaling information from multiple upstream stimuli that activate PKC or generate diacylglycerol (DAG). In addition to possessing substrate specificity similar to CaMK, PKD family members also contain a pleckstrin homology (PH) domain, differentiating them from other members of the PKC family. This allows PKDs to interact and modulate the functions of proteins involved in a multitude of signaling pathways and to disseminate information from the PKC signaling pathway as well. Further, PKD family members exhibit diverse subcellular localization (such as cytosol, membrane, nucleus, Golgi, mitochondria), allowing them to influence different signaling pathways (5-7).

The PKD family contains three members that are homologous in structure and function, namely PKD1, PKD2 and PKD3 (5-9). PKD1 is the most studied member of this family, which is also referred to by other names such as PRKD1 (to differentiate it from PKD-polycystic kidney disease) and PKC\(\mu\).
The **PKD1** gene, located on human chromosome 14q11, is broadly expressed in many organs including the thyroid, brain, heart and lungs, with highest expression in the prostate and testis germ cells (1, 3, 10). PKD1 has been shown to play important roles in a variety of cellular functions that regulate intracellular signal transduction pathways, cell survival, proliferation, motility, invasion, angiogenesis and apoptosis (1, 5-9). PKD1 also plays a critical role in the formation and consolidation of memory in the neurons (11), in cardiac cell functioning and maintenance of cardiovascular health (12), and in the regulation of the immune system (13, 14). Thus the deregulation of PKD1 has been connected with the development of cancers, cardiovascular hypertrophy and other diseases. In this review, we will focus on PKD1 and its role in cancer development and cancer cell motility.

**Structural Characteristics of PKD1**

All three members of the PKD family share distinct structural homology with each other. The human PKD1 is the largest member with 912 amino acids and a molecular weight of ~115kDa. The other two members are PKD2 with 878 amino acids (molecular weight of ~105kDa) and PKD3 (previously called PKCv/PKCnu) with 890 amino acids (molecular weight ~ 110kDa) (5). The PKD family members possess a common modular structure consisting of an N-terminal region with regulatory domains and a C-terminal region with the kinase domain (Figure 1) (reviewed by Rozengurt et al., 2005) (5). The proteins are maintained in an inactive state through auto-inhibition of the kinase domain by its regulatory domains (5). The regulatory region of PKD1 contains an alanine-proline rich region (AP domain - amino acids 17-146) at the N-terminus, followed by a cysteine rich domain (CRD - amino acids 146-320) that consists of two tandem cysteine-rich Zn-finger like domains (C1a and C1b) separated by a long spacer, an acidic amino acid rich region (AC domain - amino acids 336-390), and a pleckstrin homology domain (PH domain - amino acids 422-541) (5, 7, 15). The catalytic kinase domain present at the C-terminus extends from amino
acids 585-839 (Figure 1). The type 1 PDZ (PSD-95/Discs large/ZO-1) binding motif is present at the most C-terminal end of PKD1 (16). Both the CRD region and the PH domain play important roles in intramolecular inhibition of the kinase activity. Deletion of either of these domains or mutation of critical residues within the PH domain results in constitutively active PKD1 (5, 7). The CRD domain also binds and responds to lipid second messenger diacyl glycerol (DAG) or DAG analogue phorbol esters, and determines the membrane localization of this protein. While C1a participates in Golgi DAG binding and localization, C1b participates in high affinity DAG binding, as well as membrane and nuclear localization of the protein (5). The PH domain in PKD1 has been shown to interact with other proteins and plays a role in subcellular localization of this protein (5). The PH domain also participates in the nuclear export of PKD1. Unlike PH domains in other proteins that bind lipids, no lipid binding ability has yet been demonstrated for this domain of PKD1 (6). The type 1 PDZ binding domains of PKD1 have been shown to be essential for interaction with proteins (16, 17) and for proper surface localization of Kidins220, a PKD1 substrate molecule (16). The 3 amino acid consensus sequences, containing Ser or Thr at -2 position and a hydrophobic amino acid at zero position (S/T.X.Ф) (Ф-hydrophobic amino acid), are present at the most C-terminal end of proteins and interact with PDZ domains containing proteins (16). The human cells contain over two hundred proteins with at least a PDZ domain that appears to mainly aid in protein-protein interaction and the assembly of huge protein complexes. Thus, it is likely that the PDZ binding domain of PKD1 might plays an essential role in the proper surface localization of proteins involved in cell signaling pathways, cell-cell adhesion and cell polarization. The PDZ domain may also determine the subcellular localization of PKD1 within the cells by interacting with specific protein scaffolds.

While the regulatory regions of PKD1 include some features similar to the members of the PKC family, the catalytic domain of PKD1 possesses features distantly resembling CaMK, such as structural homology, and substrate and inhibitor specificity. The substrate consensus sequence for PKD1 is
L.X.R.(Q/K/E/M).(M/L/K/E/Q/A).S*.X.X.X.X. and unlike members of the PKC family, PKD1 exhibits a high requirement for leucine at the -5 position for substrate phosphorylation (7, 18-20). PKD2 and PKD3 also have very similar modular arrangements with minor structural differences. While PKD3 lacks an N-terminal AP rich region and a C-terminal PDZ binding domain, the N-terminus of PKD2 possesses a proline rich region instead of an AP rich region. In addition, PKD2 also contains a serine rich region in between the C1a and C1b regions of the CRD domain (5) (Figure 1).

All three members of the PKD family exhibit extensive homology within these structural domains. However, the three PKD proteins carry out independent and diverse functions due to differential subcellular localization and expression pattern in different tissues (5). PKD1 is predominantly localized in the cytoplasm, with minor quantities seen in various organelles such as the Golgi apparatus and mitochondria (6). Following stimulation of the cell, PKD1 is rapidly recruited to the cell membrane and activated. This is followed by a quick translocation of PKD1 back into the cytoplasm and its redistribution to other organelles. In contrast, PKD2 is predominantly cytoplasmic and accumulates in the nucleus following cell membrane recruitment and activation (21). PKD3, on the other hand, is both nuclear and cytoplasmic in nature, even under resting conditions (22). All three isoforms show nuclear cytoplasmic shuttling following activation, indicating critical functions as a messenger between these subcellular structures. The subtle differences in the structural organization of the isoforms, combined with their different subcellular localization and expression pattern, allows for participation of these proteins in multiple signaling pathways of various cells.

**Activation and Regulation of PKD1**

PKD1 resides primarily as an inactive kinase in the cytoplasm under resting conditions. A small fraction also exists in the Golgi apparatus (6). In certain special cell types, PKD1 has been found to have other subcellular distribution. For example, in the neurons, PKD1 has been shown to reside in transport vesicles
(23), while in B cells it has been shown to be localized at the mitochondria (6). PKD1 is activated by a number of different agents, including pharmacological agents like Bryostatin1, phorbol esters and/or physiological stimuli like tumor necrotic factor (TNF), neuropeptides, angiotension II and platelet derived growth factors (PDGF) (5, 6). Multiple mechanisms have been identified that regulate the activity of PKD1. The best characterized PKD1 activation mechanism is the phospholipase C/protein kinase C (PLC/PKC) signaling pathway (5). The activation of PLC through the engagement of surface receptors by various physiological stimuli, like neuropeptides and GPCR agonists, results in the generation of DAG, which mediates recruitment and activation of PKCs at the membrane. DAG also participates in the recruitment of PKD1 to the plasma membrane through its interaction with the C1b domain. This is followed by phosphorylation of PKD1 in the activation loop, at residues mouse Ser744 and Ser748 (equivalent to human Ser738 and Ser742), by the members of PKC family (1, 5, 7). Activation loop phosphorylation releases PH mediated inhibition of PKD1 activity and stabilizes the protein in its active form (5). Thus, biochemical studies suggest sequential steps in the activation of PKD1 by PKC as follows: the engagement of surface receptors in response to various stimuli, the generation of DAG, PKC recruitment and activation at the membrane, and finally activation of PKD1 by PKC. Activation by DAG/phorbol ester is completely suppressed in the presence of PKC inhibitors or through the mutation of active site residues in PKD1 (PKD1Ser744/748Ala) (6, 7). Conversely, replacement of both serine residues with glutamic acid (Ser744/748Glu) markedly increased activity without phorbol ester stimulation (6, 7). These results indicate activation loop phosphorylation as a key mechanism in PKD1 activation. The novel PKCs (PKCδ, PKCe, PKCη and PKCθ) have been shown to be involved in PKD1 activation (6, 7). Following phosphorylation, PKD1 rapidly transduces the DAG-PKC signals from the cell surface by quickly dissociating from the plasma membrane, relocating to the cytosol, and eventually moving to the nucleus, which is facilitated by the C1b domain of PKD1. Activation loop phosphorylation of PKD1 has
also been shown to occur on mitochondrial surface, in response to oxidative stress (6, 7). During oxidative stress conditions, mitochondrial diacyl glycerol (mDAG) generated through the action of phospholipase D1, recruits PKD1 to the mitochondrial surface through its interaction with the CRD domain (24). The recruited PKD1 is tyrosine phosphorylated by Src-Abl kinases, eventually leading to PKD1 activation by PKCδ (25).

Mechanisms other than PKC-dependent phosphorylation also appear to be involved in PKD1 activation. For example, while Ser255 of PKD1 is also phosphorylated in response to phorbol esters, the Ser255Glu PKD1 mutant is not constitutively active. Interestingly, this mutant is capable of phorbol ester mediated activation even in the presence of PKC inhibitor, indicating the existence of PKD1 activation mechanisms that do not involve PKC (1). Caspase-3 mediates activation of PKD1 by cleaving the protein between the acidic domain and PH domain, a process especially active during apoptosis induced by genotoxic drugs (1). Studies have also revealed long term activation of PKD1 by a GPCR agonist in the presence of the PKC inhibitor. The slow phase activation of PKD1 in the presence of the PKC inhibitor clearly indicates a PKC independent activation mechanism (26, 27). PKD1 activation by slow auto-phosphorylation of the Ser748 also represents another PKC independent mode of activation (28).

Several regulatory mechanisms modulate PKD1 activity, such as auto-inhibition, phosphorylation, proteolytic degradation, subcellular localization, and various cell context dependent PKD1 activation mechanisms. (1, 5-7). The auto-inhibition of PKD1 kinase activity that is mediated by the CRD and PH domain can be abrogated by interactions of these domains with other proteins, such as PKC and Gβγ, or by phosphorylation within these domains resulting in structural changes within PKD1 (5-7). Interactions with other proteins can also lead to change in subcellular localization of the protein. The activity of phosphorylated PKD1 can be attenuated by the binding of 14-3-3 proteins to the C1a regulatory domain.
resulting in altered subcellular localization of the protein (1). The differential expression of various PKC isoforms (PKCδ, PKCe, PKCη and PKCθ) that activate PKD1 determines the cell context dependent activation mechanisms that operate in a particular cell type (7). Activation of PKD1 by phosphorylation at Ser738/742 (equivalent to mouse PKD1 Ser744/748) is often followed by auto-phosphorylation at other sites, including Ser910 (equivalent to mouse PKD1 Ser916), which is a characteristic step that follows PKD1 activation (1, 5, 8). Recent evidence indicates that phosphorylation of Ser916 could be an intermolecular reaction (28). While the phosphorylation at Ser916 may play a role in structural modification of the protein and it has been used as a tool to monitor active PKD1, the role of this auto-phosphorylation is only partly recognized. For example, phosphorylation of Ser916 residue in the PDZ binding motif of PKD is essential for the interaction and appropriate localization of Kidins220 on the membrane (16). In addition, the phosphorylation of Ser916 has also been suggested to have a potential role in terminating/stunting PKD1 mediated substrate phosphorylation, since the Ser916Ala mutant shows increased resistance to proteolysis and dephosphorylation (28, 29).

**Cancer Related Signaling Pathways Modulated by PKD1:**

PKD1 modulates a diverse array of signaling pathways and therefore regulates multiple biological functions critical for the normal functioning of the cell. Some of the biological functions regulated by PKD1 are (a) DNA synthesis, chromatin remodeling and cell proliferation (b) cell-cell adhesion, cell polarization, migration and invasion, (c) apoptosis (d) detoxification of oxidative stress signal (e) Golgi organization and transport of vesicle from trans-Golgi network (f) angiogenesis (g) immune cell response and (h) insulin secretion and survival of pancreatic β cells (1, 9). As a downstream component of the PLC/PKC pathway, PKD1 integrates signaling from multiple stimulating factors and activates diverse downstream substrates/pathway. Thus its deregulation affects a multitude of signaling pathways, resulting in diseases
like cancer, cardiovascular hypertrophy and diabetes. In this section, we will briefly discuss the signaling pathways modulated by the aberrant expression of PKD1 in cancer (Figure 2).

**Modulation of Mitogen Activated Protein Kinase (MAPK) pathway by PKD1**

Aberration in MAPK signaling pathway is associated with the development and progression of many types of cancer (30). Activation of various surface receptors, such as the G protein coupled receptors (GPCR), by their ligands results in activation of the MAPK pathway. Different lines of evidence also support a role for GPCR in the development and progression of many types of cancers (5, 30). GPCR agonists activate PKD1 in many different cell types. Activation of Swiss 3T3 cells overexpressing PKD1 by GPCR agonist results in prolonged activation of the MEK/ERK/RSK pathway compared to cells overexpressing kinase dead mutant PKD1. This role for PKD1 in activating the MAPK pathway occurs possibly through the phosphorylation of RIN1 (a competitive Ras effector protein), resulting in sustained stimulation of the Ras/Raf/MEK/ERK/RSK pathway (reviewed in Jaggi et al., 2007 and Van Lint et al., 2002) (1, 6). The resulting accumulation of c-Fos leads to increased DNA synthesis, cell cycle progression and cell proliferation (8). This pathway is prominently seen in pancreatic cancer cells (8).

The long term activation of the c-Jun N-terminal kinase (JNK) pathway by the epidermal growth factor (EGF) results in phosphorylation of Ser63 residue of c-Jun and induction of apoptosis (31). While PKD1 was found to directly interact and phosphorylate c-Jun at its N-terminus, it has also been implicated to decrease apoptosis via modulation of JNK functions and suppression of c-Jun phosphorylation (5, 6). The outcome of PKD1 mediated downregulation of the JNK signaling pathway is dependent on the cell type and the stimulus (6, 26). For example, this pathway is activated upon exposure to hydrogen peroxide, but not ceramide or TNF-α induced cell death (1). Also, while attenuation of JNK signaling was observed following overexpression of PKD1 in HEK cells, this was not observed in A549 non-small cell lung carcinoma cells.
In addition, while PKD1 mediated inhibition of this pathway appears to play a prominent role in pancreatic cancer cell line survival (33), PKD1 was found to enhance apoptosis in the renal tubular epithelial cells by activating JNK (34). Thus, more studies are required to understand the contrasting outcome of PKD1 mediated activation of the JNK pathway in different cell types.

**Activation of NFκB by PKD1**

The NFκB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) transcription factors are heterodimeric proteins that play critical roles in regulating stress induced inflammatory and immune responses. Mutation in the NFκB gene has been linked to enhanced cell survival and proliferation in various cancers (25). PKD1 acts as a sensor for mitochondrial oxidative stress and regulates the cellular response by activating the NFκB pathway (25). PKD1 activates NFκB by the phosphorylation and activation of IKK (Inhibitory Kappa Kinase) (25). This results in the degradation of inhibitory protein IκB, the release of NFκB from the inhibitory complex, followed by accumulation in the nucleus and induction of downstream target genes (25), which in turn causes cell survival, cell proliferation and inflammation (8, 35). PKD1 may also be involved in IKK independent mechanisms that activate the NFκB pathway within the cells (25). PKD1 mediated NFκB activation has been demonstrated in different cell lines, including immune cells, intestinal epithelial cells and lung cells (8). However, only PKD1 activation following tyrosine phosphorylation is capable of activating the NFκB pathway, perhaps pointing to specific requirements, including specific structural changes in PKD1 that may be necessary for NFκB activation (25). More work is needed to understand and establish the underlying structural requirements and functional mechanism involved in PKD1 mediated NFκB activation.
Modulation of Androgen Receptor Signaling by PKD1

The Androgen receptor (AR) is a ligand dependent transcription factor present in many cell types (36). The binding of AR to its ligand (androgen hormones) leads to the translocation of the AR-ligand complex into the nucleus, where it binds to ARE (androgen response elements) regions in the DNA to trigger transcription of various downstream genes involved in cell survival and proliferation (36). In prostate cancer, somatic mutation in AR results in progression of tumor from an androgen sensitive (AS) stage to an androgen insensitive (AI) stage that is refractory to androgen depletion treatment (36). Recently, it has been demonstrated that PKD1 exists in a transcription complex along with AR and a promoter sequence for prostate specific antigen (PSA) in prostate cancer cells (37). PKD1 negatively regulates the function of AR in prostate cancer cells as the overexpression of wildtype PKD1 or kinase-dead PKD1 attenuates ligand-dependent AR function. Alternatively, PKD1 knockdown enhances ligand dependent AR activity (37). Studies have also revealed that PKD1 interacts and phosphorylates Ser82 residue of Hsp27 (a molecule that is necessary for nuclear translocation of AR) and represses AR functions in prostate cancer cells (38). The AR function is also modulated by interaction with other proteins, like β-catenin, which augments AR functions (39). Since PKD1 interacts and down regulates both nuclear β-catenin and AR transcription activity, deregulated expression of PKD1 may play a critical role in the initiation and progression of prostate cancer (1, 40-42). Further understanding of modulation of AR signaling by PKD1 at the molecular level will facilitate the developing of new strategies for the treatment of prostate cancer.

Regulation of Histone Deacetylases by PKD1

The DNA binding proteins, histones, controls protein expression by regulating the access of transcription factors to DNA sequence. Orchestrated acetylation of lysine residues by histone acetyl transferase (HAT) and its deacetylation by histone deacetylase (HDAC) enzymes determine the epigenetic regulation of genes
Deacetylation of lysine residues of histones by HDACs results in a tighter chromatin structure and transcriptional repression of genes. Aberrant histone deacetylation has been found to correlate with pathological gene repression and neoplastic transformation (43). PKD1 modulates the phosphorylation and transportation of class II HDACs (HDAC 5 and 7) from the nucleus to the cytoplasm, which in turn, mitigates transcriptional repression of silenced genes (1, 5). PKD1 activated in endothelial cells by VEGF (Vesicular Endothelial Growth Factor) phosphorylates HDAC5 at Ser259/498 and induces cell proliferation and angiogenesis (44). Studies have also revealed that the phosphorylation of HDAC7 at Ser178, Ser344, and Ser479 by PKD1 causes transcription of angiogenic genes (45). PKD1 mediated modulation of HDACs has also been shown to play an essential role in B cell response and muscle formation by regulating transcription activity of myocyte enhancer factor-2 (9). These studies implicate a vital role for PKD1 in HDACs modulation. However, further understanding of this pathway would help delineate the role of PKD1 in epigenetic regulation.

PKD1 modulates cell polarity and cell adhesion

Recent studies have suggested an important role for PKD1 in maintaining cell polarity and a critical role in enhancing cell-cell adhesion and decreasing motility. Cellular polarization is critical for differentiation, proliferation and tissue homeostasis, a characteristic that is lost in cancer cells. Par (partitioning-defective) proteins are highly conserved serine-threonine kinases that play a critical role in maintaining cell polarity. PKD1 was recently demonstrated to phosphorylate Par1B and thereby regulate its presence on the membrane (46). Thus modulating the levels or function of PKD1 might be important role for maintaining cell polarity.

The adhesion complex formed by the E-cadherin-β-catenin complex plays a vital role in maintaining cell-cell contact (1). Also, the aberrant expression and distribution of these proteins have been associated with
cancer (1, 40). In addition to its role in cell adhesion, β-catenin functions as a co-tanscription factor with TCF (T-cell factor) and plays an important role in the Wnt signaling pathway. Aberrant subcellular localization of β-catenin in the nucleus leads to enhanced transcription of genes like c-myc and cyclin D1, resulting in oncogenic transformation of the cells. In prostate cancer cells, PKD1 modulates E-cadherin and β-catenin function (1, 42, 47). Studies from our laboratory have demonstrated that PKD1 interacts, phosphorylates, and modulates the functions of E-cadherin resulting in increased cell-cell adhesion and decreased cellular motility, implicating a pivotal role of PKD1 in prostate cancer progression and metastasis (47). Our studies have also demonstrated that PKD1 directly interacts, phosphorylates, and alters the functions of β-catenin (42). The activation of PKD1 by Bryostatin1 decreased nuclear β-catenin and also enriched membrane localization of β-catenin, resulting in increased cellular aggregation and decreased motility (42). Thus, activation of PKD1 inhibits the oncogenic signals produced by β-catenin’s co-transcription factor activity. Interestingly, both β-catenin and E-cadherin, like PKD1, have been shown to be aberrantly expressed in prostate cancer (40, 48). In addition to prostate cancer cells, PKD1 also seems to play an important role in cell adhesion in other cancer cell types. For example, in the MDA-MB-435 breast cancer cell line, PKD1 enhanced cell adhesion following stimulation with cis-polyunsaturated fatty acids (49). Moreover, PKD1 also regulated cell adhesion by directly interacting with focal adhesion molecule α-v-β-3 and promoted its localization at focal adhesion sites (49). These studies suggest that PKD1 may be a potential target for therapeutic intervention to prevent cancer cell metastasis.

PKD1 in Actin Remodeling and Cell Migration

Dynamic remodeling of actin cytoskeleton is crucial for cell motility and migration, and plays a central part not only in pathological conditions, like cancer metastasis, but also in a variety of normal biological processes like morphogenesis and wound healing. Accumulating evidence suggests a prominent role for
PKD1 as a negative regulator of cell motility/migration through F-actin reorganization (42, 50-53). The dynamic and complex process of actin remodeling involves the synergistic action of a number of proteins active in the polymerization of actin and depolymerization/severing of actin polymer to generate actin monomer for further polymerization (53). Succinctly, actin monomer nucleation attracts a number of actin binding proteins that allow the elongation and formation of F-actin filaments. However, the process is limited by the availability of G-actin monomers that are generated through the severing of F-actin by an actin depolymerizing factor (ADF/cofilin) (53). The activity of cofilin is negatively regulated by LIMKinase and positively regulated by Slingshot phosphatases (SSH). This process not only releases actin monomers that are recycled for polymerization at the leading edge, but also produces a new barbed end that promotes further growth and branching of F-actin fiber by the binding of the Arp2/3 complex. The process of nucleation and branching is enhanced by cortactin and WASP proteins and the newly generated actin filaments at the branch points form the membrane protrusion that enables cell motility (53).

PKD1 has been shown to directly interact with F-actin, and activated PKD1 co-localizes at the leading edge following activation of a signal transduction cascade (50). In various cancer cell line models, including breast, prostate and pancreatic cancer, inhibition of PKD1 function by the overexpression of kinase inactive PKD1 or siRNA mediated inhibition shows enhanced cell migration, while overexpression of PKD1 shows reduced migration, implicating a prominent role of PKD1 in cell migration (42, 50-52). Dissection of the mechanism revealed that activated PKD1 not only co-localizes at the leading edge, but also binds to and phosphorylates a number of actin interacting proteins like cortactin, Arp2/3, and Slingshot like 1 (SSH-1L) phosphatase which subsequently inhibits actin polymerization. (50, 52, 54). In PKD1 mediated modulation of many actin binding proteins, the modus operandii seems to involve phosphorylation induced structural change in the proteins, exposing the 14-3-3 protein binding site within these proteins. This allows quick binding, sequestration and translocation of these proteins from the leading edge into the cytoplasm by the
protein 14-3-3 (54-56). This mechanism of action was very clearly demonstrated in the PKD1 mediated phosphorylation and regulation of cortactin at Ser298 (56). Following its phosphorylation, cortactin was unavailable for participation in lamellipodia extension due to its translocation into the cytoplasm from the leading edge. In addition, the overexpression of phosphorylation-deficient cortactin-S298A protein in pancreatic cancer cells resulted in enhanced lamellipodia extension and directed cell migration due to faster Arp-cortactin mediated synergistic actin polymerization, underscoring a negative role for PKD1 in cell migration (56). Contrary to this, De Kimpe et al. have shown that PKD1 phosphorylation of cortactin, at Ser298 and Ser348, does not result in subcellular changes in cortactin localization nor does it affect lysophosphatidic acid (LPA) induced cell migration (57). The process of actin severing is carried out by activated cofilin and requires the function of SSH-1L phosphatase. The phosphorylation of SSH1L by PKD1 structurally modulates the protein, thereby generating a 14-3-3 binding site and subsequent sequestration into cytoplasm, resulting in SSH-1L and thus cofilin inactivation (55). Therefore, activators of PKD1 indirectly reduce the levels of active cofilin. While further analysis is required to establish the role of PKD1 in cell motility, the overwhelming evidence has been toward the involvement of PKD1 in the modulation of proteins involved in actin remodeling. As a result, this protein could play a very important role in cell migration and cancer metastasis.

**PKD1 in Cancer**

The role of PKD1 in cancer is not surprising due to its involvement in many cellular functions such as cell proliferation, apoptosis, cell adhesion, invasion, and vesicle trafficking (1). Similar to the intricate roles played by many kinases, PKD1 has a complex relationship with respect to cancer development. PKD1 has been shown to be downregulated in prostate cancer (41, 58), breast cancer (52), gastric cancer (59) and colon cancer (60). However, the overexpression of PKD1 has been demonstrated to play a role in the
development of pancreatic cancer (61) and skin cancers (62, 63) (Table 1). Therefore, the consequence of upregulation or downregulation of PKD1 in cancer development is dependent on the tissue type. Since PKD1 functions as a critical kinase that integrates extracellular signals into intracellular processes by modulating a multitude of signaling pathways, the regulation of PKD1 levels and/or activity through pharmacological or genetic intervention might aid in cancer treatment (Figure 3). The expression pattern of PKD1 in different cancers and its role in cancer development are discussed in this section.

PKD1 in Prostate Cancer

Prostate cancer is one of the leading causes of cancer-related deaths in men in the United States. While early detection of prostate cancer has greatly decreased the mortality rate, it is often fatal at later stages due to the progression of cancer from an androgen dependent (AD) to androgen independent (AI) phenotype, for which there are no effective treatments. The highest expression of PKD1 is observed in the prostate tissues, suggesting a crucial role of this protein in normal prostate functions (64). Studies from our laboratory and others suggest important roles for PKD1 in prostate cancer development and metastasis. Immunohistochemical (IHC) analyses revealed severe downregulation of PKD1 in prostate cancer cells and an incremental decrease in PKD1 expression following progression from AD to AI prostate cancer (41). Additionally, an androgen independent C4-2 cell line has shown significantly lowered PKD1 expression compared to androgen dependent LNCaP prostate cancer cells. These data suggest a potential role of PKD1 in the progression of prostate cancer from an AD to AI state (41). Furthermore, our studies demonstrate that PKD1 interacts, phosphorylates, and positively regulates the functions of E-cadherin and β-catenin (cadherin-catenin complex) enhancing cell-cell adhesion and decreasing cellular motility, strongly implying a major role for PKD1 in prostate cancer progression and metastasis (42, 47). Activated PKD1 also decreases nuclear β-catenin levels, resulting in the attenuation of oncogenic signaling by β-catenin’s co-
transcription factor activity. Additionally, while overexpression of PKD1 and E-cadherin suppresses cancer cell phenotype, simultaneous co-expression of PKD1 and E-cadherin in prostate cancer cells results in a cumulative decrease in cancer phenotypes. These data strongly support a pivotal role of PKD1 in prostate cancer (51). Recent studies in xenograft mouse models with PKD1 overexpressing prostate cancer cells revealed significantly reduced tumor growth compared to control, supporting a tumor suppressor role of PKD1 (65).

PKD1 also interacts and modulates the function of androgen receptor (AR) in prostate cancer cells (37, 38, 51). This is especially significant given that ARs are ligand dependent transcription factors that play a critical role in prostate biology and carcinogenesis (36). Studies with overexpression or knockdown cell line models of PKD1 demonstrate that PKD1 negatively modulates the function of AR (37) through the modulation of Hsp27 mediated AR functions (38). Additionally, PKD1 has also been found to be involved in the invasion of prostate cancer cells via modulation of matrix metalloproteinase (MMP)-2 and MMP-9 (66) or metallothionin 2A, a protein involved in cell proliferation and chemo-resistance of cancer cells (67, 68). A recent study has revealed a vital role of PKD1 in epithelial-mesenchymal transition (EMT) by modulating the function of transcription factor snail, a central regulator of EMT (65). PKD1 phosphorylates the Ser11 residue of snail, resulting in nuclear export of this protein and thus alterations in the expression of proteins involved in EMT (65).

Despite all the accumulating evidence implicating a tumor suppressor function for PKD1 in prostate cancer growth, invasion, and metastasis, other studies suggest upregulation of PKD1 and PKD3 in prostate cancer (69, 70). IHC analysis of patient tissue samples revealed upregulation of PKD1 and PKD3, compared to control samples (70). Inhibition of PKD kinase activity using chemical inhibitors with higher specificity for PKD family members revealed inhibition of cell proliferation, motility and invasion (65, 66). These data
indicate an oncogenic role for PKD family members in prostate cancer, although experimental evidence generated in studies using inhibitors are fraught with errors due to cross reactivity with other kinases (66, 69, 70). While PKD3 overexpression has been shown to enhance the tumorigenicity of prostate cancer cells by enhancing the ERK1/2 and AKT signaling pathways, the molecular basis for the oncogenic role of PKD1 has not at all been probed in prostate cancer cells (65). In addition, another independent study also indicates a pro-oncogenic role for PKD1 in prostate cancer (48). Experiments with prostate cell lines overexpressing Wnt5a suggest the involvement of PKD1 in establishing enhanced cell migration and invasion (48). Inhibition of PKD1 suppressed Wnt5a dependent cell migration and invasion (48). Hence, further involved investigations, including analyses of proteomic, metabolomic changes and IHC analyses in a large cohort of human prostate cancer samples are necessary to unequivocally establish the pro or anti-cancer role of this protein in prostate cancer.

**PKD1 in Breast Cancer**

Breast cancer affects both males and females and is one of the leading causes of cancer related deaths in females. While only 10-15% of breast cancers are due to inherited genetic mutations (mutations in BRCA1 and BRCA2), the majority of incidences occur due to somatic mutations that result in uncontrolled cell proliferation and metastasis. Recent accumulating evidence suggests a potential role of PKD1 in breast cancer progression (52). Tissue microarray analysis showed that while PKD1 was highly expressed in ductal epithelial cells of the normal breast tissues, its expression was significantly reduced in 95% of all the 40 invasive breast cancer tissue samples. Of importance, no change in PKD2 and PKD3 levels were observed, indicating an important role for PKD1 function in breast cancer. In breast cancer cell lines, PKD1 expression was detected only in non-invasive or minimally invasive breast cancer cell lines like MCF-7, while no or low expression was detected in highly invasive cell lines like MDA-MB-231 (9, 52). This
suppression was attributed to DNA methylation which supports the involvement of epigenetic mechanisms in breast cancer progression (52). In 2D and 3D cell culture models, PKD1 expression was shown to drastically alter the invasive and proliferative ability of breast cancer cells (52). At the molecular level, PKD1 has been shown to interact with cortactin and paxillin at invadopodia (71), and inhibit cellular motility and invasion in breast cancer cells via phosphorylation and inactivation of the SSH1L protein (50, 52, 54). Additionally, PKD1 was found to suppress the expression of many pro-invasion matrix metalloproteinases (MMPs) like MMP-2, MMP-7, MMP-9, MMP-10, MMP-11, MMP-13 and MMP-14 (52). Interestingly, PKD1 has recently been implicated in EMT via inhibition of snail functions and modulation of mesenchymal-epithelial markers like vimentin and E-cadherin (65). Thus re-expression or activation of PKD1 might serve as a potential therapeutic strategy for breast cancer treatment.

**PKD1 in Gastro-Intestinal tract Cancers**

Research from our laboratory and others has suggested a negative role for PKD1 in the development of gastrointestinal (GI) tract cancers (59, 60). In gastric carcinoma, PKD1 was found to be downregulated in over 70% of cell lines and in about 60% of patient tissue samples (59). Target specific silencing of PKD1 using siRNA increased the invasion and motility of gastric carcinoma cells, confirming a negative role for PKD1 in gastric cancer. PKD1 was found to be epigenetically downregulated in gastric cancer cells expressing low levels of PKD1 (59). In colon cancer tissues, IHC analysis revealed downregulation of PKD1 in about 70% of higher Dukes stages (II, III and IV), moderately and poorly differentiated colon cancer samples compared to non-neoplastic colon samples (60). The overexpression of PKD1 in SW480 colon cancer cells inhibits nuclear β-catenin accumulation and reduces β-catenin/TCF transcriptional activity, suggesting a suppressive role of PKD1 in colon cancer (60). On the other hand, a recent study revealed an important role for PKD1 in potentiating Cox-2 production in colonic myofibroblasts following
TNF-α and lysophosphatidic acid treatment, implicating a role for PKD1 in modifying the tumor microenvironment to promote tumor growth (72). Thus, thorough investigations are warranted to confirm the role of PKD1 in GI tract malignancies.

**PKD1 in Pancreatic Cancer**

Pancreatic cancer is one of the most aggressive cancers and is highly resistant to cancer chemotherapy. The overexpression of PKD1 has been revealed to play a role in pancreatic cancer progression (8). Using the PANC-1 human pancreatic ductal adenocarcinoma cell line as a model system, Guha et al. 2002 and 2003, showed the involvement of a functional PKD1 signaling pathway in mitogenic signals initiated by neurotensin (NT) (61, 73). *In-vitro* and *in-vivo* assays following NT treatment revealed rapid PKC dependent activation of PKD1, which in turn led to rapid activation of MAPK/ERK kinase 1 (MEK1/2), activation and nuclear translocation of extracellular signal regulated kinase 1 and 2 (ERK-1 and ERK-2), and eventually increased DNA synthesis (61, 73). PKD1, ERK-1 and ERK-2 activation was inhibited by specific PKC inhibitors bisindolylmaleimide 1 (GF109203X, also called Gö6850) and bisindolylmaleimide IX (Ro31-8220), implicating the involvement of a PKC/PKD signaling process in human ductal pancreatic carcinoma cells (61, 73). IHC analyses of a small cohort of tissue samples revealed the overexpression of PKD1 in pancreatic cancer compared to normal pancreatic tissues (32). The overexpression of PKD1 has been attributed to confer enhanced proliferation and higher anti-apoptotic activity to the pancreatic cancer cells. The overexpression of PKD1 in the Colo357 pancreatic cancer cell line, that shows low PKD1 expression, not only decreased sensitivity of the cells to CD95-mediated apoptosis, but also enhanced cell growth and telomerase activity, suggesting a correlation between PKD1 expression and resistance to apoptosis (32). The anti-apoptotic proteins c-FLIPL and survivin were upregulated in PKD1 overexpressing cells and their enhanced presence could be a possible reason for the pro-survival role of PKD1 in pancreatic...
cells. Inhibition of the PKC/PKD pathway in these PKD1 overexpressing cells using the broad spectrum PKC/PKD inhibitor, Gö6983, restored the sensitivity of cells to apoptosis, suggesting a pro-carcinogenic role for this protein in pancreatic malignancy (8, 32). A recent \textit{in-vitro} and \textit{in-vivo} animal study using a new PKD1 specific small-molecule inhibitor (CRT0066101) has shown inhibition of pancreatic cancer growth, suggesting the development of PKD1 inhibitors as a novel therapeutic target for treatment of pancreatic cancer (74).

**PKD1 in Skin Cancer and Other Cancers**

Basal cell carcinoma (BCC) is the most common type of skin cancer in the world. Aberrant distribution and upregulation of PKD1 has been shown to be associated with BCC and neoplastic mouse keratinocytes, suggesting a putative role of PKD1 in skin cancer (63). More specifically, PKD1 was found to be associated with repression of keratinocyte differentiation and upregulation of cell proliferation, possibly through the involvement of the ERK/MAPK pathway (75). In-vitro analysis of primary mouse keratinocytes exposed to UVB radiation (a key risk factor for development of BCC) revealed activation of PKD1 by the Src tyrosine kinase family, without the involvement of the canonical PKC activation pathway (76). Overexpression of wild-type PKD, but not mutant PKD, attenuated UVB induced apoptosis, implicating a role of PKD1 in BCC (76). The role of PKD1 in the development of other cancers is not well defined. However, some experimental evidence implicates PKD1 in the development of certain types of cancers. For example, the rapid activation of PKD1 by PKCs was detected in small cell lung carcinoma (SCLC) cell lines in response to treatment with phorbol esters or diffusable DAG. This suggests a possible role of PKD1 in the conversion of external carcinogenic stimuli into an intracellular response in SCLC (77). PKDs might also play a role in renal cell carcinoma and metastasis (34). Using a combination of PKC and PKD inhibitors, Brenner et al have shown a role for PKDs in the initial steps of tumor progression by regulating the adhesion of renal
carcinoma cells to endothelial cells (34). Studies on human malignant lymphoma cells revealed no detectable levels of PKD1 in these tissues, while PKD2 expression was documented, with no change in expression level in either normal or malignant tissues. However, further studies are necessary to confirm the role of PKD1 in skin and other cancers and to unveil the mechanisms behind its deregulated expression.

Conclusions

PKD1 is emerging as an important molecule in cancer development. Since many types of cancer show dysregulation of PKD1 expression, it is being explored as a biomarker for cancer diagnosis and prognosis. While the outcome of PKD1 deregulation seems to be dependent on the type of tissues presenting aberrant levels of PKD1, pharmacological interference to regulate PKD1 levels might prove to be an important additional tool to treat cancer. Thus, regulation of PKD1 levels and/or activity might aid cancer treatment due to its role as a critical kinase that integrates extracellular signals into intracellular processes. The active role of PKD1 in cell motility, actin cytoskeleton remodeling and EMT suggests its potential involvement in cancer metastasis. Further understanding of the molecular basis of PKD1 deregulation and the contrasting outcome of this deregulation in various tissues will help to strategically design and formulate novel targeted therapies for cancer treatment.

Authors’ contributions

VS drafted the manuscript. SCC and MJ participated in revising the manuscript. All authors have read and approved the final manuscript.

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Table 1. PKD1 expression and its roles in various cancers. Comprehensive representation of the role of PKD1 and the prominent signaling pathways modulated in various cancers.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Cancer Type</th>
<th>PKD1 Status</th>
<th>Modulated Signaling pathway</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast cancer</td>
<td>Downregulated</td>
<td>MMPs</td>
<td>Eisler et al 2009 (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Actin remodeling and cell motility</td>
<td>Peterburs et al 2009 (54)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>EMT</td>
<td>Du et al 2011 (65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Downregulated</td>
<td>AR signaling</td>
<td>Mak et al 2008 (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSP27</td>
<td>Hassan et al 2010 (38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EMT</td>
<td>Du et al 2011 (65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ERK/MAPK/MMPs</td>
<td>Biswas et al 2010 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upregulated</td>
<td></td>
<td>Chen et al 2008 (70)</td>
</tr>
<tr>
<td>3</td>
<td>Gastro-intestinal cancer</td>
<td>Downregulated</td>
<td>β-catenin</td>
<td>Kim et al 2008 (59)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Cox-2</td>
<td>Jepperson et al 2009 (60)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Rodriguez Perez et al 2011 (72)</td>
</tr>
<tr>
<td>4</td>
<td>Pancreatic cancer</td>
<td>Upregulated</td>
<td>Ras/Raf/MEK/ERK/RSK</td>
<td>Guha et al 2002, 2003 (61, 73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSP27</td>
<td>Yuan et al 2009 (78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EGF/JNK</td>
<td>Kisfavi et al 2010 (33)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Apoptosis</td>
<td>Trauzold et al 2003 (79)</td>
</tr>
<tr>
<td>5</td>
<td>Basal cell cancer</td>
<td>Upregulated</td>
<td>ERK/MAPK</td>
<td>Ristich et al 2006 (63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apoptosis</td>
<td>Jadali et al 2010 (75)</td>
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<td>Arun et al 2010 (76)</td>
</tr>
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**Figure Legends**

**Figure 1. Molecular structure of Protein Kinase D.** The Protein Kinase D (PKD) family members possess an N-terminal regulatory region and a C-terminal catalytic domain. The schematic representation shows the modular structure of PKD family members and the major functions carried out by the domains. PKD1 is the largest member with 912 amino acids, while PKD2 contains 878 amino acid residues and PKD3 contains 890 amino acids. All the three PKDs show high degree of homology within the various domains. However, only PKD1 and PKD2 contain an alanine-proline or proline rich region at the N-terminus, and a PDZ binding domain at the C-terminus. The numbers represent amino acid positioning of each domain in human PKD1, PKD2 and PKD3. The Serine residues marked in the kinase domain represent the activation loop residues phosphorylated by nPKC members. The highly homologous mouse PKD1 contains 918 amino acids, while mouse PKD2 is made of 875 amino acids and mouse PKD3 contains 889 amino acids. AP-Alanine proline rich domain; C1a and C1b- Cystein rich domain 1a and 1b; AC- Acidic domain; PH- Pleckstrin homology domain; Kinase- Kinase domain; PB- PDZ binding domain; P- Proline rich region; S- Serine rich region.

**Figure 2. Schematic representation of signaling pathways modulated by Protein Kinase D1 (PKD1) in cancer.**

The deregulated expression of Protein Kinase D1 (PKD1) results in the development of cancer. The schematic representation depicts the pathways that activate PKD1 and the various downstream pathways and functions modulated by this kinase (represented by maroon ovals). The activation of various membrane receptors like G-protein coupled receptor (GPCR) and other growth factor receptors (GR) leads to the
activation of PKD1 by the Phospho Lipase C-Protein Kinase C (PLC-PKC) pathway through the formation of diacyl glycerol (DAG). DAG modulates PKD1 function by binding and quickly recruiting it to the cell-membrane for activation by PKCs. PKD1 can also be activated by the Golgi Gβγ-PKCε in the Golgi apparatus, proteolytic cleavage by Caspase3 (Casp3), by oxidative stress resulting in PKD1 activation on mitochondrial surface through the action of SRC-Abl kinase and PKCδ, by UVB rays activated SRC kinase and by PKC independent self activation mechanism. Activated PKD1 is rapidly translocated from the membrane to cytoplasm and eventually to the nucleus where it regulates downstream pathways. Activated PKD1 also regulates the process of vesicle trafficking from the Golgi to the membrane that eventually controls cell surface proteins that are involved in cell adhesion, cell polarity and motility. Depending on the cell types, PKD1 either functions as a tumor suppressor or as an oncogene within the cell. 2A. Tumor suppressor functions of PKD1. PKD1 has been shown to inhibit cancer in prostate, breast and gastrointestinal tract. PKD1 inhibits tumorigenesis by enhancing cell adhesion and inhibiting the function of proteins involved in cell migration, cell invasion, cell proliferation, and in EMT (epithelial mesenchymal transition). PKD1 phosphorylates E-cadherin and β-catenin and thereby enhances cell-cell adhesion. PKD1 helps in maintaining cellular polarity by phosphorylating Par-1 polarity associated kinase and thereby enhancing its cytoplasmic sequestration by 14-3-3 protein. Activated PKD1 also helps in establishing cell polarity by positively regulating the trans-Golgi network (TGN) carriers to the basolateral membrane. Activated PKD1 can also inhibit the transcriptional activity of β-catenin and androgen receptor (AR) resulting in reduced cell proliferation. It also inhibits EMT (epithelial-mesenchymal transition) via regulating the activity of snail transcription factor. PKD1 negatively regulates cell invasion by influencing the levels of matrix metalloproteinases (MMPs) through the modulation of HDACs (histone deacetylases). It also negatively regulates actin remodeling and thus cell motility through the phosphorylation of slingshot-1 like protein (SSH-1L) and cortactin. 2B. Pro-oncogenic role of PKD1. PKD1 upregulation has been linked
to the development of pancreatic and skin cancer and may be in prostate cancer (controversial). Some of the pathways modulated by PKD1 that might result in pro-oncogenic role is as follows. Activated PKD1 enhances cell survival and proliferation by enhancing DNA synthesis and upregulating the function of Erk1/2 protein (Extracellular Signal Regulated Kinase) in the mitogen activated protein kinase (MAPK) pathway leading to the accumulation of c-Fos. Activated PKD1 decreases apoptosis by suppressing the function of JNK (c-Jun N-terminal Kinase) pathway resulting in decreased c-Jun levels. Under oxidative stress condition, PKD1 enhances cell survival through the activation of the NFκB pathway. PKD1 expression contributes to oncogenesis by enhancing angiogenesis via regulating of the activity of histone deacetylase’s activity (HDAC 5 and 7). (TCF-T-cell factor; IKK-I Kappa Kinase, Hsp27-Heat shock protein 27).

Figure 3: Proposed mode of actions of PKD1 modulators in cancer therapeutics: PKD1 is aberrantly regulated in many cancers. It is down regulated in prostate, breast and gastro-enteric cancers and upregulated in pancreatic and skin cancers. Targeted suppression of PKD1 in pancreatic and skin cancer, using siRNA or specific small molecule inhibitors might aid cancer treatment by modulating NFκB, Erk (Extracellular Signal Regulated Kinase), JNK (c-Jun N-terminal Kinase) and HDAC (Histone Deacetylases) signaling. In contrast, tumor specific delivery of PKD1 gene or PKD1 activators may be useful for prostate, breast and gastro-enteric cancer treatment. This will suppress androgen receptor (AR) and β-catenin signaling, invasion, motility, epithelial mesenchymal transition (EMT) and enhance cell-cell adhesion via increased E-cadherin, β-catenin localization at the membrane. Pathways activated following treatment are shown in green boxes, whereas pathways inhibited are shown in red boxes.
Figure 1.
Figure 2. PKD1 in cancer.

2A. Tumor suppressor functions of PKD1

2B. Oncogenic functions of PKD1
Molecular Cancer Research

Emerging Roles of Protein Kinase D1 in Cancer

Vasudha Sundram, Subhash C Chauhan and Meena Jaggi

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