## Phylogeny

Protein kinase D1 (PRKD1) was initially classified as an atypical member of the protein kinase C (PKC) family, named PKCμ, but was later reclassified into the distinct PKD family based on structural and kinase domain sequence analysis (sundram2011emergingrolesof pages 1-3, rykx2003proteinkinased pages 1-2). Sources conflict on its broader kinome group classification. Several sources place PRKD1 within the Ca2+/calmodulin-dependent protein kinase (CAMK) superfamily, based on kinase domain sequence similarities (johnson2023anatlasof pages 4-4, gilles2021developmentsinthe pages 1-3, rykx2003proteinkinased pages 1-2, sundram2011emergingrolesof pages 1-3). In contrast, the foundational kinome analysis by Manning et al. (2002) and other reports classify PRKD1 within the AGC group of kinases (manning2002theproteinkinase pages 1-2, lint2002proteinkinased pages 1-2).

The PKD family consists of three isoforms in humans: PKD1, PKD2, and PKD3 (gilles2021developmentsinthe pages 1-3, rykx2003proteinkinased pages 1-2). PRKD1 is evolutionarily conserved with orthologs identified in multiple species, including mice (Mus musculus), rats (Rattus norvegicus), flies (Drosophila melanogaster), worms (Caenorhabditis elegans), and yeast (Saccharomyces cerevisiae) (sundram2011emergingrolesof pages 1-3).

## Reaction Catalyzed

PRKD1 is a serine/threonine kinase that catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins (sundram2011emergingrolesof pages 3-4).

## Cofactor Requirements

The catalytic activity of PRKD1 requires Mg2+ as a cofactor (sundram2011emergingrolesof pages 3-4).

## Substrate Specificity

Based on a comprehensive kinome-wide analysis, PRKD1 is classified as a basophilic kinase (johnson2023anatlasof pages 4-4). Its substrate recognition motif is characterized by a preference for basic residues, specifically arginine (R), at the -3 or -2 positions relative to the phosphorylated serine or threonine residue (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 4-4).

## Structure

PRKD1 is a multi-domain protein of approximately 912 amino acids (zhang2021multifacetedfunctionsof pages 1-2). Its modular structure includes an N-terminal regulatory region and a C-terminal kinase domain (steinberg2012regulationofprotein pages 1-2). The regulatory region contains a ubiquitin-like domain (ULD) implicated in dimerization, tandem cysteine-rich C1 domains (C1a and C1b) that bind diacylglycerol (DAG), and a pleckstrin homology (PH) domain that mediates autoinhibition (zhang2021multifacetedfunctionsof pages 2-4, zhang2021multifacetedfunctionsof pages 1-2). The C-terminus contains the catalytic kinase domain and a PDZ-binding motif involved in substrate recognition (zhang2021multifacetedfunctionsof pages 2-4, sundram2011emergingrolesof pages 1-3).

An experimentally determined crystal structure for PRKD1 is unavailable; however, its 3D structure is understood through homology modeling and the AlphaFold model (unknownauthors2013pkd13dstructure pages 10-17, zhang2021multifacetedfunctionsof pages 2-4). The kinase domain adopts a conserved bi-lobed catalytic core architecture with an ATP-binding cleft between the N- and C-terminal lobes (unknownauthors2013pkd13dstructure pages 17-24). Key structural features within the kinase domain include the C-helix in the N-lobe, which is crucial for positioning catalytic residues for ATP binding, and a hydrophobic spine, a set of conserved hydrophobic residues spanning both lobes that stabilizes the active conformation of the kinase (steinberg2012regulationofprotein pages 1-2, zhang2021multifacetedfunctionsof pages 2-4, unknownauthors2013pkd13dstructure pages 17-24).

## Regulation

PRKD1 is allosterically regulated by the direct binding of diacylglycerol (DAG) to its tandem C1a and C1b domains (cobbaut2018functionandregulation pages 3-4). Upon generation by phospholipase C (PLC), DAG recruits cytosolic PRKD1 to cellular membranes (fu2011proteinkinased pages 1-2, zhang2021multifacetedfunctionsof pages 2-4). This binding event induces a conformational change that relieves an intramolecular autoinhibitory mechanism mediated by the N-terminal regulatory region, particularly the PH domain (cobbaut2018functionandregulation pages 2-3, fu2011proteinkinased pages 1-2, steinberg2012regulationofprotein pages 1-2).

This membrane localization and conformational opening primes PRKD1 for trans-phosphorylation by upstream protein kinase C (PKC) isoforms (e.g., novel PKCs δ, ε, θ, η) (rozengurt2011proteinkinased pages 1-2, fu2011proteinkinased pages 1-2). PKC phosphorylates critical serine residues in the activation loop of PRKD1—Ser738 and Ser742 in human (equivalent to Ser744/Ser748 in mouse)—which stabilizes the active conformation and leads to full kinase activation (gilles2021developmentsinthe pages 1-3, fu2011proteinkinased pages 1-2, steinberg2012regulationofprotein pages 1-2). Phosphorylation at Ser738 by PKC triggers autophosphorylation at the adjacent Ser742 (zhang2021multifacetedfunctionsof pages 2-4). Following activation, PRKD1 autophosphorylates at Ser910 in its C-terminus, a modification which further modulates its activity (cobbaut2018functionandregulation pages 2-3, steinberg2012regulationofprotein pages 1-2).

PRKD1 can also be activated by oxidative stress via tyrosine phosphorylation by Abl and Src kinases at sites within the PH domain and N-terminus (gilles2021developmentsinthe pages 1-3). Nucleocytoplasmic shuttling is regulated by phosphorylation at Ser244 by casein kinase 1 (CK1) (zhang2021multifacetedfunctionsof pages 22-23).

## Function

PRKD1 is ubiquitously expressed in human tissues, with the highest expression reported in prostate and testis germ cells (sundram2011emergingrolesof pages 1-3). The kinase localizes to multiple cellular compartments, including the cytoplasm, plasma membrane, Golgi apparatus, mitochondria, and nucleus, where it phosphorylates numerous substrates to regulate diverse signaling pathways (gilles2021developmentsinthe pages 1-3, zhang2021multifacetedfunctionsof pages 2-4).

PRKD1 is activated downstream of stimuli that engage GPCRs or receptor tyrosine kinases, leading to PLC-dependent DAG production and PKC activation (rozengurt2011proteinkinased pages 1-2). Known substrates of PRKD1 include class IIa histone deacetylases (HDACs), such as HDAC5, which are excluded from the nucleus upon phosphorylation (lavalle2010proteinkinased pages 4-5, rozengurt2011proteinkinased pages 8-9). Other substrates include cardiac troponin I, myosin binding protein C, CREB, phosphatidylinositol-4 kinase IIIβ (PI4KIIIβ) at the Golgi, and the actin-remodeling proteins SSH1L and EVL-1 (rozengurt2011proteinkinased pages 8-9, zhang2021multifacetedfunctionsof pages 22-23, lavalle2010proteinkinased pages 4-5). It interacts with proteins such as AKAP-Lbc, paxillin, and cortactin (rozengurt2011proteinkinased pages 8-9, lavalle2010proteinkinased pages 4-5).

Functionally, PRKD1 regulates a wide array of biological processes, including cell proliferation, survival, apoptosis, motility, vesicle trafficking, and angiogenesis (rozengurt2011proteinkinased pages 1-2, lavalle2010proteinkinased pages 4-5). It acts as a key regulator of cardiac hypertrophy and fibrosis and is involved in oxidative stress responses through NF-κB activation (gilles2021developmentsinthe pages 1-3, zhang2021multifacetedfunctionsof pages 22-23).

## Inhibitors

The development of small-molecule inhibitors for PRKD1 has yielded specifically designed bioactive molecules, including compounds from the benzothienothiazepinone class (gilles2021developmentsinthe pages 1-3, bravoaltamirano2011synthesisandstructure−activity pages 4-5). As PRKD1 activation requires upstream phosphorylation by PKC, its activity is also blocked by PKC inhibitors that do not directly target PRKD1’s catalytic activity (rozengurt2011proteinkinased pages 1-2).

## Other Comments

Dysregulated PRKD1 signaling is associated with pathological conditions including various cancers (pancreatic, breast, skin), cardiac hypertrophy, and other cardiovascular diseases (gilles2021developmentsinthe pages 1-3, zhang2021multifacetedfunctionsof pages 1-2). In cancer, its role can be context-dependent; PRKD1 expression is epigenetically silenced in highly invasive breast cancer cells, while in pancreatic cancer it is overexpressed and linked to proliferation (lavalle2010proteinkinased pages 4-5). Recurrent PRKD1 mutations have been reported in breast and colon cancers (rozengurt2011proteinkinased pages 8-9). Global knockout of PRKD1 in mice results in embryonic lethality, indicating an essential biological role (rozengurt2011proteinkinased pages 8-9).

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