## Phylogeny

Protein kinase D1 (PRKD1) was first described as an atypical member of the protein kinase C family (PKC µ) but, on the basis of sequence and domain organisation, is now placed in the separate PKD family (Sundram et al., 2011; Rykx et al., 2003). Disagreement remains over its higher-order kinome classification: several studies group PKD with Ca²⁺/calmodulin-dependent protein kinases (CAMK) (Johnson et al., 2023; Gilles et al., 2021; Rykx et al., 2003; Sundram et al., 2011), whereas the seminal kinome survey by Manning et al. (2002) and related work place it in the AGC kinase group (Manning et al., 2002; Van Lint et al., 2002). Humans encode three PKD isoforms (PKD1–3) (Gilles et al., 2021; Rykx et al., 2003). Orthologues of PRKD1 occur in mouse, rat, Drosophila, Caenorhabditis elegans and Saccharomyces cerevisiae, underscoring broad evolutionary conservation (Sundram et al., 2011).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Sundram et al., 2011).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Sundram et al., 2011).

## Substrate Specificity

Kinome-wide profiling classifies PRKD1 as a basophilic kinase. Preferred motifs contain a basic residue, typically arginine, at the –3 or –2 position relative to the target Ser/Thr (Johnson et al., 2023).

## Structure

PRKD1 is a ~912-residue, multi-domain enzyme with an N-terminal regulatory region (ubiquitin-like domain, tandem C1a/C1b diacylglycerol-binding domains and an autoinhibitory pleckstrin-homology domain) followed by a C-terminal kinase domain and PDZ-binding motif (Zhang et al., 2021; Steinberg, 2012; Sundram et al., 2011). No experimental crystal structure is available; homology modelling and AlphaFold predict the canonical bi-lobed kinase fold with an ATP-binding cleft, correctly positioned C-helix and a hydrophobic spine stabilising the active state (Unknown Authors, 2013; Steinberg, 2012; Zhang et al., 2021).

## Regulation

• Allosteric activation: diacylglycerol binding to C1a/C1b recruits PRKD1 to membranes and relieves autoinhibition by the PH domain (Cobbaut & Van Lint, 2018; Fu & Rubin, 2011).  
• Activation-loop phosphorylation: membrane-associated novel PKC isoforms phosphorylate Ser738 and subsequently Ser742, culminating in full activation; PRKD1 then autophosphorylates Ser910 (Gilles et al., 2021; Fu & Rubin, 2011; Steinberg, 2012; Zhang et al., 2021).  
• Alternative inputs: oxidative stress activates PRKD1 via Abl/Src-mediated tyrosine phosphorylation; CK1 phosphorylation of Ser244 modulates nuclear–cytoplasmic shuttling (Gilles et al., 2021; Zhang et al., 2021).

## Function

PRKD1 is ubiquitously expressed, with highest levels in prostate and testis germ cells (Sundram et al., 2011). It localises to cytoplasm, plasma membrane, Golgi, mitochondria and nucleus (Gilles et al., 2021; Zhang et al., 2021). Activation commonly follows GPCR or receptor tyrosine kinase signalling that generates diacylglycerol and activates PKC (Rozengurt, 2011). Documented substrates include class IIa histone deacetylases (e.g., HDAC5), cardiac troponin I, myosin-binding protein C, CREB, PI4KIIIβ, and actin regulators SSH1L and EVL-1 (Rozengurt, 2011; Zhang et al., 2021; LaValle et al., 2010). Interacting partners comprise AKAP-Lbc, paxillin and cortactin (Rozengurt, 2011; LaValle et al., 2010). Through these targets PRKD1 controls cell proliferation, survival/apoptosis, motility, vesicle trafficking, angiogenesis, cardiac hypertrophy and oxidative-stress-induced NF-κB activation (Rozengurt, 2011; Zhang et al., 2021).

## Inhibitors

Selective small-molecule inhibitors have been developed, notably benzothienothiazepinone derivatives (Gilles et al., 2021; Bravo-Altamirano et al., 2011). Indirect inhibition arises from PKC inhibitors that prevent the activating phosphorylation of PRKD1 (Rozengurt, 2011).

## Other Comments

Aberrant PRKD1 signalling is linked to pancreatic, breast and skin cancers, cardiac hypertrophy and other cardiovascular disorders (Gilles et al., 2021; Zhang et al., 2021). In breast cancer PRKD1 is often epigenetically silenced, whereas it is overexpressed in pancreatic cancer (LaValle et al., 2010). Recurrent oncogenic PRKD1 mutations occur in breast and colon tumours (Rozengurt, 2011). Global Prkd1 knockout in mice is embryonically lethal, indicating essential developmental functions (Rozengurt, 2011).

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