1. Phylogeny  
   Serine/threonine‐protein kinase D3 (PRKD3), also known as PKD3, PKC nu type, or EPK2, is a member of the protein kinase D (PKD) family. The family comprises three isoforms (PKD1, PKD2, and PKD3), and PRKD3 shows high evolutionary conservation across mammalian species with orthologs evident in multiple vertebrate lineages (avkiran2008proteinkinased pages 1-2, novozhylov2017bioinformaticsearchfor pages 7-8). Analysis of the catalytic domain indicates that PRKD3 shares over 90% amino acid identity with other family members such as PKD1 and PKD2, placing it within a well‐conserved branch of Ca²⁺/calmodulin‐dependent protein kinases that has been retained throughout eukaryotic evolution (avkiran2008proteinkinased pages 1-2, piscuoglio2016lackofprkd2 pages 1-2). The phylogenetic context reveals that the PKD subfamily is distinct from classical protein kinase C isoforms despite functional interactions; it is positioned within a larger kinase superfamily that includes members of the AGC and CAMK groups. These evolutionary relationships underscore the core signaling role that the PKD family plays in transducing second messenger signals, and PRKD3 is recognized as one of the more recently studied members in terms of its disease associations and functional contributions (avkiran2008proteinkinased pages 1-2, novozhylov2017bioinformaticsearchfor pages 7-8).
2. Reaction Catalyzed  
   PRKD3 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to the hydroxyl group of serine or threonine residues on substrate proteins. In chemical terms, the reaction is represented as: ATP + [protein]–(L‑serine or L‑threonine) → ADP + [protein]–(L‑serine/threonine‑phosphate) + H⁺. This phosphorylation event modifies the function or localization of the substrate protein and is central to PRKD3’s role in signal transduction (avkiran2008proteinkinased pages 1-2).
3. Cofactor Requirements  
   The kinase activity of PRKD3 is dependent on the presence of Mg²⁺ ions. Like many other kinases that utilize ATP, the binding of Mg²⁺ facilitates the proper coordination of the phosphate groups on ATP during the phosphoryl transfer reaction. No additional cofactors have been specified beyond the essential requirement for divalent cations such as Mg²⁺ (avkiran2008proteinkinased pages 1-2).
4. Substrate Specificity  
   Substrate recognition by PRKD3 is dictated by sequence motifs surrounding the serine/threonine phosphorylation sites. Evidence from structural and biochemical analyses indicates that protein kinase D isoforms tend to recognize a consensus that involves an aliphatic residue at the –5 position and a basic amino acid, such as arginine, at the –3 position relative to the phosphorylated residue (avkiran2008proteinkinased pages 2-3). In addition, substrates phosphorylated by PRKD3 typically exhibit flanking basic residues that help mediate electrostatic interactions with the catalytic cleft. Although a fully defined motif for PRKD3 has not been exhaustively delineated, the emerging consensus is that a phosphorylatable serine or threonine with adjacent arginine and lysine residues provides optimal recognition for phosphorylation by PRKD3 (avkiran2008proteinkinased pages 2-3, castillo2019análiseestruturalde pages 19-23).
5. Structure  
   PRKD3 is a modular protein composed of distinct domains that contribute to its regulatory and catalytic functions. The N-terminal portion contains regulatory elements, including two cysteine-rich, zinc finger–like domains that bind diacylglycerol (DAG) and phorbol esters, and a pleckstrin homology (PH) domain that plays a critical role in subcellular localization and autoinhibition. The C-terminal region of the protein encompasses the catalytic kinase domain responsible for its serine/threonine phosphorylation activity. This catalytic domain is organized into a bilobal structure characteristic of protein kinases, with an N-terminal lobe rich in β‐strands and a C-terminal lobe that is predominantly α‐helical (avkiran2008proteinkinased pages 1-2, pei2023computationalanalysisof pages 2-4). Within the catalytic domain, key structural features include the activation loop, which requires phosphorylation for full activity, a conserved DFG motif that coordinates divalent cations, and a C-helix that plays an essential role in aligning catalytic residues. The autoinhibitory conformation imposed by the PH domain is relieved upon binding of DAG and subsequent phosphorylation events, allowing the alignment of the hydrophobic spine and other catalytic motifs necessary for efficient enzymatic activity (avkiran2008proteinkinased pages 7-7, pei2023computationalanalysisof pages 2-4). The overall three‐dimensional organization of PRKD3 thus integrates lipid-mediated regulatory signals with a robust catalytic machinery that is highly conserved among the PKD family members.
6. Regulation  
   The regulatory mechanisms controlling PRKD3 activity are multifaceted and rely primarily on phosphorylation events. Activation of PRKD3 occurs following translocation to membrane compartments enriched in diacylglycerol (DAG), where interaction with DAG-binding cysteine-rich domains and the PH domain facilitates recruitment. Once localized at the membrane, PRKD3 is phosphorylated by upstream novel protein kinase C (PKC) isoforms at specific serine residues within its activation loop. This PKC-mediated phosphorylation relieves the autoinhibitory influence of the PH domain and enables autophosphorylation events that fully activate the kinase (avkiran2008proteinkinased pages 4-5). Additional regulatory layers include post-translational modifications such as caspase-3-mediated cleavage under conditions of genotoxic stress and tyrosine phosphorylation mediated by Src/Abl family kinases in response to oxidative stimuli. These phosphorylation events modulate not only the catalytic activity but also affect the subcellular localization of PRKD3, allowing its nuclear translocation and interactions with proteins such as 14-3-3 which further influence its signaling output (avkiran2008proteinkinased pages 7-7). Regulatory inputs conveyed through receptor-mediated signals and changes in the intracellular DAG pool establish diverse mechanisms by which the activity of PRKD3 is finely tuned in the cellular context.
7. Function  
   PRKD3 functions as a central mediator in the conversion of transient diacylglycerol (DAG) signals into prolonged cellular responses. By phosphorylating serine/threonine residues on downstream substrates, PRKD3 orchestrates a number of critical cellular processes. These include regulation of vesicular transport, cell migration, proliferation, and survival. In cardiovascular cells, for instance, PRKD3 has been implicated in modulating myocardial contractility through the phosphorylation of substrates such as cardiac troponin I and class II histone deacetylases, thereby contributing to contractile function and hypertrophic responses (avkiran2008proteinkinased pages 4-5, avkiran2008proteinkinased pages 7-7). In addition, PRKD3 plays a role in promoting resistance to oxidative stress, a function that is inferred by similarity with other family members and is reflected in its ability to integrate signals downstream of PKC activation (OpenTargets Search: -PRKD3). Recent studies have also highlighted a role for PRKD3 in cancer biology, with increased expression correlating with aggressive phenotypes in malignancies such as triple‐negative breast cancer and prostate cancer. PRKD3 modulates oncogenic signaling pathways by phosphorylating key substrates involved in cell cycle progression and apoptosis, thereby impacting processes related to tumor growth and metastasis (lv2021smallmoleculeinhibitortargeting pages 1-2, zhang2021multifacetedfunctionsof pages 30-30). Overall, the function of PRKD3 is integrated into diverse signaling networks where it acts as a convergent point for lipid-based second messenger signals and kinase cascades that govern cellular homeostasis and disease-relevant pathways.
8. Other Comments  
   Several small-molecule inhibitors have been developed that target PKD isoforms, including PRKD3, as part of efforts to modulate its activity in disease contexts. Among these, multi-kinase inhibitors such as MIDOSTAURIN have been shown to inhibit PRKD3 alongside other related kinases, and are currently in advanced clinical phases for use in neoplastic conditions (OpenTargets Search: -PRKD3). In addition, compounds such as CRT0066101, CID755673, and bipyridyl-based inhibitors (BPKDi) have been reported to inhibit PKD activity in cellular and preclinical models, with potential applications in both oncology and cardiovascular disease (lv2021smallmoleculeinhibitortargeting pages 4-5, wang2022smallmoleculeinhibitors pages 5-6). Disease association studies have linked PRKD3 to several pathological conditions including acute myeloid leukemia, mast-cell leukemia, and cardiovascular risk phenotypes such as systolic blood pressure and body mass index (OpenTargets Search: -PRKD3). Further, overexpression of PRKD3 has been observed in aggressive cancers, including triple-negative breast cancer, where its activity contributes to enhanced cell proliferation, migration, and invasion (lv2021smallmoleculeinhibitortargeting pages 1-2, lv2021smallmoleculeinhibitortargeting pages 5-6). These findings have spurred interest in the development of more selective inhibitors and in the clinical evaluation of PRKD3 as a therapeutic target. The integration of phosphoproteomic data further underscores the potential of PRKD3 as a key node in signaling networks that are amenable to pharmacological intervention (karamafrooz2021integratedphosphoproteomicsfor pages 31-32).
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