## Phylogeny

Protein kinase C zeta (PKCζ/PRKCZ) is a member of the AGC superfamily of kinases, which also includes Protein Kinase A (PKA) and Protein Kinase G (PKG) (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2003proteinkinasecζ pages 1-1). The AGC superfamily contains approximately 60 members (garciaconcejo2021proteinkinasec pages 1-2). PRKCZ is classified within the atypical PKC (aPKC) subfamily, one of four subgroups of the mammalian PKC family alongside classical (cPKC), novel (nPKC), and PKC-related (PKN) kinases (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2012theatypicalpkcs pages 19-23, yao2012splicevariantprkcζprc pages 6-7). This classification is based on domain structure and functional attributes (unknownauthors2012theatypicalpkcs pages 19-23). The aPKC subfamily in jawed vertebrates consists of two genes: PKCζ (PRKCZ) and PKCι (PRKCI) (garciaconcejo2021proteinkinasec pages 7-10). PKCζ shares approximately 72% sequence homology with PKCι/λ (wilhelm2011allostericmodulatorsdirected pages 32-36).

## Reaction Catalyzed

PRKCZ is a serine/threonine kinase that catalyzes the phosphorylation of serine and threonine residues on substrate proteins (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2012theatypicalpkcs pages 19-23). The reaction involves the transfer of a phosphate group from ATP to the hydroxyl group of a serine or threonine residue (unknownauthors2003proteinkinasecζ pages 1-1, unknownauthors2012theatypicalpkcs pages 13-15).

## Cofactor Requirements

The catalytic activity of PRKCZ is independent of calcium (Ca2+) and diacylglycerol (DAG) (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2012theatypicalpkcs pages 1-2). Activation requires phosphatidylserine (PS) (garciaconcejo2021proteinkinasec pages 1-2). Other lipid cofactors involved in its activation include phosphatidylinositol (3,4,5)-trisphosphate (PIP3), phosphatidic acid, ceramide, and arachidonic acid (unknownauthors2003proteinkinasecζ pages 1-1, wilhelm2011allostericmodulatorsdirected pages 32-36). The kinase requires ATP as the phosphate donor and divalent metal ions such as Mg2+ or Mn2+ for phosphoryl transfer (unknownauthors2012theatypicalpkcs pages 13-15, wilhelm2011allostericmodulatorsdirected pages 39-42).

## Substrate Specificity

The provided context does not explicitly mention the substrate consensus motif or amino acid preferences for PRKCZ (silnitsky2023anupdateon pages 3-5, unknownauthors2012theatypicalpkcs pages 1-2).

## Structure

While computational tools such as AlphaFold are referenced for exploring PKC modulator interactions, the provided sources do not offer direct characterization details of the 3D structure for Q05513 (PRKCZ) (silnitsky2023anupdateon pages 3-5). PRKCZ is an atypical PKC isoform characterized by a unique domain organization, distinguishing it from conventional PKCs (unknownauthors2012theatypicalpkcs pages 1-2). It lacks the calcium-responsive C2 domain and possesses an atypical C1 domain with a single zinc-finger structure, rendering it insensitive to DAG and phorbol esters (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2012theatypicalpkcs pages 1-2, wilhelm2011allostericmodulatorsdirected pages 32-36). A defining feature is an N-terminal Phox/Bem1 (PB1) domain, which mediates protein-protein interactions with partners like p62 and PAR-6 (garciaconcejo2021proteinkinasec pages 1-2, unknownauthors2003proteinkinasecζ pages 3-3, unknownauthors2012theatypicalpkcs pages 1-2). The protein also contains a pseudosubstrate domain involved in regulation and a C-terminal catalytic kinase domain (wilhelm2011allostericmodulatorsdirected pages 32-36). This kinase domain includes an ATP-binding region with a critical lysine (Lys-281) required for catalytic activity (unknownauthors2003proteinkinasecζ pages 1-1). aPKCs have an acidic phosphomimetic residue in their hydrophobic motif that allows them to bypass the need for phosphorylation at that site for activation (unknownauthors2012theatypicalpkcs pages 1-2).

## Regulation

PRKCZ activation requires phosphorylation at key serine/threonine residues for stabilization (unknownauthors2012theatypicalpkcs pages 1-2). Phosphorylation at Thr-410 in the activation loop by phosphoinositide-dependent kinase 1 (PDK1) is a critical step, which is facilitated by the binding of PIP3 to PRKCZ and leads to a subsequent phosphorylation at Thr-560 (unknownauthors2003proteinkinasecζ pages 3-3, unknownauthors2012theatypicalpkcs pages 1-2). The mammalian target of rapamycin complex 2 (mTORC2) is another upstream kinase that phosphorylates and activates PRKCZ (unknownauthors2012theatypicalpkcs pages 1-2). Both PIP3 binding and PDK1-mediated phosphorylation are required for stable activation and to relieve PS-dependent autoinhibition (unknownauthors2003proteinkinasecζ pages 3-3). Activity is also controlled by protein-protein interactions; the inhibitor protein Prostate apoptosis response-4 (Par-4) binds to the C1 domain of PRKCZ to inhibit its activity (unknownauthors2003proteinkinasecζ pages 3-3, unknownauthors2012theatypicalpkcs pages 19-23).

## Function

PRKCZ is a serine/threonine kinase involved in diverse cellular processes, including NF-κB activation, cell polarity, migration, proliferation, inflammatory responses, and the maintenance of long-term potentiation (LTP) (unknownauthors2003proteinkinasecζ pages 4-4, unknownauthors2003proteinkinasecζ pages 4-5, unknownauthors2012theatypicalpkcs pages 1-2).

PRKCZ is activated downstream of receptors such as the IL-1 receptor (IL-1R), nerve growth factor receptor (NGFR), and tumor necrosis factor receptor (TNFR) (unknownauthors2003proteinkinasecζ pages 4-4). It functions downstream of PI3K, with upstream activating kinases including PDK1 and mTORC2 (unknownauthors2003proteinkinasecζ pages 1-1, unknownauthors2012theatypicalpkcs pages 1-2). In the NF-κB pathway, PRKCZ phosphorylates and activates the IκB kinase (IKK) complex by binding to IKKβ (unknownauthors2003proteinkinasecζ pages 4-4, unknownauthors2012theatypicalpkcs pages 4-5). It also directly phosphorylates the RelA (p65) subunit of NF-κB at Ser311, a modification crucial for recruiting the coactivator CBP and displacing the repressive histone methyltransferase GLP, thereby promoting transcription (unknownauthors2012theatypicalpkcs pages 19-23, wilhelm2011allostericmodulatorsdirected pages 32-36).

PRKCZ also participates in the MAPK cascade by activating MEK1-ERK1/2 and can act as an adapter for EGF-induced ERK5 activation (unknownauthors2003proteinkinasecζ pages 3-3). It phosphorylates PKB/Akt at a C-terminal serine and contributes to insulin-stimulated GLUT4 translocation (unknownauthors2003proteinkinasecζ pages 3-3, wilhelm2011allostericmodulatorsdirected pages 36-39). In the immune system, it is essential for IL-4-mediated activation of Stat6 during Th2 differentiation (unknownauthors2012theatypicalpkcs pages 8-9).

PRKCZ forms signaling complexes through its PB1 domain with proteins such as p62/ZIP, PAR-3, PAR-6, and NBR1 (unknownauthors2003proteinkinasecζ pages 3-3, unknownauthors2012theatypicalpkcs pages 1-2). The ZIP/p62 protein links PRKCZ to TNFα, IL-1, and NGF receptor complexes via TRAF proteins and RIP (unknownauthors2003proteinkinasecζ pages 3-3). It also interacts with the neuron-specific protein FEZ1 to stimulate neurite elongation (unknownauthors2003proteinkinasecζ pages 4-4).

## Inhibitors

PRKCZ activity is inhibited by the endogenous protein Prostate apoptosis response-4 (Par-4), which binds to its C1 domain (unknownauthors2003proteinkinasecζ pages 3-3, unknownauthors2012theatypicalpkcs pages 19-23). Experimental inhibitors used to study its function include a myristoylated PKCζ pseudosubstrate peptide and the compound chelerythrine, both of which impair LTP (unknownauthors2003proteinkinasecζ pages 4-5). Broad-spectrum staurosporine-derived PKC inhibitors, such as Enzastaurin and Midostaurin, target multiple PKC isoforms including PKCζ (wilhelm2011allostericmodulatorsdirected pages 36-39).

## Other Comments

Dysregulation of PRKCZ is associated with multiple human diseases (wilhelm2011allostericmodulatorsdirected pages 36-39). It is implicated in inflammatory and autoimmune diseases, asthma, allergic airway inflammation, and various cancers, including prostate, lung, endometrial, leukemia, and lymphoma (unknownauthors2012theatypicalpkcs pages 8-9, unknownauthors2012theatypicalpkcs pages 19-23, wilhelm2011allostericmodulatorsdirected pages 36-39). PRKCZ is also involved in metabolic diseases; it plays a role in obesity-induced inflammation and insulin resistance, and its knockout in mice causes a hyperinflammatory state and glucose intolerance due to increased IL-6 production (unknownauthors2012theatypicalpkcs pages 8-9, wilhelm2011allostericmodulatorsdirected pages 36-39). In oncology, alterations of the chromosomal locus 8p22 where PRKCZ is located have been noted in malignant tumors like esophageal and prostate cancer (unknownauthors2003proteinkinasecζ pages 4-4). A specific splice variant, PRKC-z-PrC, is selectively expressed in prostate cancer cells and has been proposed as a biomarker for the disease (yao2012splicevariantprkcζprc pages 9-10).

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