Phylogeny  
Protein kinase C zeta (PKCζ/PRKCZ) belongs to the AGC protein-kinase superfamily and, within it, to the atypical PKC (aPKC) subfamily that also contains PKCι/λ (PRKCI) (Garcia-Concejo & Larhammar, 2021; Unknown authors, 2012). In jawed vertebrates only two aPKC genes (PKCζ and PKCι) are present, and PKCζ shares ≈72 % sequence identity with PKCι (Garcia-Concejo & Larhammar, 2021; Wilhelm, 2011).

Reaction Catalyzed  
ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Garcia-Concejo & Larhammar, 2021; Unknown authors, 2012).

Cofactor Requirements  
Catalysis requires divalent metal ions (Mg²⁺ or Mn²⁺) (Unknown authors, 2012; Wilhelm, 2011). Activity is independent of Ca²⁺ and DAG but is promoted by phosphatidylserine and other lipids such as PIP₃, phosphatidic acid, ceramide, and arachidonic acid (Garcia-Concejo & Larhammar, 2021; Unknown authors, 2003; Wilhelm, 2011).

Substrate Specificity  
No consensus phosphorylation motif or residue preferences were reported in the supplied sources (Silnitsky et al., 2023; Unknown authors, 2012).

Structure  
PKCζ contains an N-terminal PB1 domain for protein–protein interactions, an atypical single zinc-finger C1 domain (lacking Ca²⁺-responsive C2), a pseudosubstrate region, and a C-terminal catalytic kinase domain that bears an essential Lys-281 in the ATP-binding site (Garcia-Concejo & Larhammar, 2021; Unknown authors, 2003; Unknown authors, 2012; Wilhelm, 2011). An acidic, phosphomimetic residue within its hydrophobic motif obviates the need for phosphorylation at that position (Unknown authors, 2012). No experimental 3-D structure of human PKCζ was provided; computational tools such as AlphaFold have been referenced for modelling (Silnitsky et al., 2023).

Regulation  
Activation requires phosphorylation of Thr-410 in the activation loop by PDK1, facilitated by PIP₃ binding, followed by phosphorylation at Thr-560 (Unknown authors, 2003; Unknown authors, 2012). mTORC2 also phosphorylates and activates PKCζ (Unknown authors, 2012). Phosphatidylserine binding relieves autoinhibition, whereas the endogenous inhibitor Par-4 binds the C1 domain to suppress activity (Unknown authors, 2003; Unknown authors, 2012).

Function  
PKCζ participates in NF-κB activation, cell polarity, migration, proliferation, inflammatory responses, and long-term potentiation (Unknown authors, 2003; Unknown authors, 2012). It acts downstream of PI3K and receptors such as IL-1R, NGFR, and TNFR, with upstream kinases PDK1 and mTORC2 (Unknown authors, 2003; Unknown authors, 2012). PKCζ phosphorylates IKKβ and RelA (Ser311) in the NF-κB pathway, activates MEK1–ERK1/2, serves as an adaptor for EGF-induced ERK5 activation, phosphorylates Akt, and is required for IL-4-mediated Stat6 activation during Th2 differentiation (Unknown authors, 2003; Unknown authors, 2012; Wilhelm, 2011). Through its PB1 domain it forms complexes with p62/ZIP, PAR-3, PAR-6, and NBR1, and interacts with neuronal FEZ1 to promote neurite elongation (Unknown authors, 2003; Unknown authors, 2012).

Inhibitors  
Endogenous: Prostate apoptosis response-4 (Par-4) (Unknown authors, 2003; Unknown authors, 2012).  
Experimental: Myristoylated PKCζ pseudosubstrate peptide and chelerythrine impair LTP (Unknown authors, 2003). Broad-spectrum staurosporine derivatives Enzastaurin and Midostaurin inhibit multiple PKCs including PKCζ (Wilhelm, 2011).

Other Comments  
Dysregulated PKCζ activity is linked to inflammatory and autoimmune disorders, asthma, obesity-induced insulin resistance, and numerous cancers (Unknown authors, 2012; Wilhelm, 2011). Chromosome 8p22 alterations encompassing PRKCZ are observed in malignant tumours, and a prostate-cancer-specific splice variant (PRKC-ζ-PrC) has been proposed as a disease biomarker (Yao et al., 2012).

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