1. Phylogeny  
   Protein kinase C zeta type (PKCζ), encoded by the PRKCZ gene and identified as Q05513, is a member of the atypical subgroup of the Protein Kinase C (PKC) family that belongs to the AGC kinase superfamily. Unlike conventional and novel PKCs, which are characterized by their dependence on calcium and diacylglycerol (DAG) for activation, PKCζ is distinguished by its evolutionary divergence; it lacks functional C2 domains and contains only a single, atypical C1 domain that does not bind DAG, thereby establishing its independent regulatory mechanism. Phylogenetic analyses trace its origin back to a common eukaryotic ancestor, with orthologs conserved among mammalian species and other eukaryotes, and it is closely related to other AGC kinases such as Akt and PDK1, forming part of a core signaling module that emerged early in evolutionary history (newton2001proteinkinasec pages 1-2, newton2018proteinkinasec pages 1-3).
2. Reaction Catalyzed  
   PKCζ catalyzes the ATP-dependent phosphorylation of serine and threonine residues present in protein substrates. The general chemical reaction can be formulated as:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This fundamental reaction underpins its ability to modulate various signaling pathways (newton1995proteinkinasec pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of PKCζ is dependent on the presence of magnesium ions (Mg²⁺), which facilitate the proper coordination of ATP within the active site. In contrast to classical PKCs, PKCζ does not require calcium ions (Ca²⁺) or diacylglycerol for its activation, reflecting its atypical nature and unique regulatory mechanism (newton1995proteinkinasec pages 1-2, newton2018proteinkinasec pages 1-3).
4. Substrate Specificity  
   PKCζ preferentially phosphorylates serine/threonine residues within its target proteins and contributes to the modulation of several signaling cascades. Although a detailed consensus motif for PKCζ is not as extensively characterized as those for higher‐resolution kinases, available evidence indicates that substrate recognition often involves the presence of proximal basic residues adjacent to the phosphorylated serine or threonine. Functionally, PKCζ phosphorylates substrates involved in the mitogen-activated protein kinase (MAPK) cascade—such as components of the MAP2K1/MEK1-MAPK1/ERK2 pathway—and has been reported to modify proteins such as β-Catenin and Yap, which are integral to cell polarity and transcriptional control (yeo2017phosphorylatedproteinkinase pages 7-7, aquino2023proteinkinasec pages 22-24).
5. Structure  
   The overall structure of PKCζ is organized into a modular architecture consisting of an N-terminal regulatory region and a C-terminal catalytic kinase domain. The regulatory region contains a PB1 (Phox and Bem1) domain that mediates specific protein–protein interactions with scaffold proteins such as p62/ZIP and PAR6; these interactions are critical for the spatial regulation of kinase activity. In addition, PKCζ harbors an atypical C1 domain that, unlike its classical counterparts, does not bind DAG, and it includes an autoinhibitory pseudosubstrate region that occupies the substrate-binding cleft under basal conditions. The catalytic domain exhibits the common bilobal kinase fold with a small N-terminal lobe primarily responsible for ATP binding and a larger C-terminal lobe that binds substrates, and it contains conserved motifs such as the nucleotide-binding P-loop and an activation loop that is constitutively phosphorylated. A notable structural feature of PKCζ is its hydrophobic motif, which contains a phosphomimetic glutamic acid residue replacing the serine/threonine phosphorylation site found in other PKC isoforms; this unique feature circumvents the need for further phosphorylation at that motif and is central to its regulation (newton2018proteinkinasec pages 3-4, newton2018proteinkinasec pages 4-6, parker2014atypicalproteinkinase pages 2-4).
6. Regulation  
   The regulation of PKCζ is achieved predominantly through phosphorylation and protein–protein interactions. Key phosphorylation events occur on the activation loop (for example, at Thr410) through the activity of phosphoinositide-dependent kinase 1 (PDK1), and on the turn motif (for example, at Thr560) through mechanisms involving the mTOR complex 2 (mTORC2); these phosphorylation steps are constitutive, ensuring that PKCζ remains catalytically competent (newton2018proteinkinasec pages 27-28, newton1995proteinkinasec pages 1-2). The autoinhibitory pseudosubstrate sequence within the regulatory domain maintains the kinase in an inactive conformation until binding of scaffold proteins such as p62 and PAR6 via the PB1 domain displaces the pseudosubstrate, thereby relieving inhibition. Additionally, regulation is further fine-tuned by interactions with lipid cofactors such as phosphatidylserine and phosphatidic acid, and under certain cellular conditions, redox modifications may also modulate its activity; however, unlike many kinases, PKCζ is not activated by calcium or DAG (newton2018proteinkinasec pages 27-28, silnitsky2023anupdateon pages 18-19).
7. Function  
   PKCζ fulfills a multifaceted role in intracellular signaling by acting as a critical mediator downstream of phosphoinositide 3-kinase (PI3K). It participates in the activation of several MAP kinase cascades; for example, following mitogenic stimuli or lipopolysaccharide (LPS) treatment in macrophages, PKCζ functions downstream of PI3K to activate the MAP2K1/MEK1-MAPK1/ERK2 signaling pathway independently of RAF1 activation. In addition, PKCζ is required for the insulin-dependent activation of AKT3 and contributes to the process of glucose transporter (GLUT4) translocation in adipocytes, thereby facilitating glucose uptake. In EGF-stimulated cells, PKCζ has been shown to bind and activate the MAP2K5/MEK5-MAPK7/ERK5 cascade independently of its catalytic activity, and it can also contribute to the activation of JUN signaling. Beyond its role in mitogenic and metabolic pathways, PKCζ is involved in the regulation of cell proliferation, cell polarity, and the inflammatory response, and it plays a part in the maintenance of long-term potentiation (LTP) in neuronal systems. These diverse functions are mediated by its ability to phosphorylate key substrates, such as β-Catenin and Yap, which in turn impact gene expression and cellular differentiation processes (aquino2023proteinkinasec pages 22-24, yeo2017phosphorylatedproteinkinase pages 7-7, newton2018proteinkinasec pages 27-28).
8. Other Comments  
   Small-molecule inhibitors targeting PKCζ have been under investigation due to its emerging role in diseases such as cancer, metabolic disorders, and cardiovascular conditions. For example, certain indazole–benzimidazole derivatives have been reported to selectively inhibit atypical PKCs by interfering with the catalytic domain or disrupting PB1 domain-mediated protein interactions. Altered expression and activity of PKCζ have been associated with oncogenic processes, including aberrant activation of NF-κB and modifications in cell polarity that contribute to tumor progression and metastasis. In addition, changes in its signaling dynamics have been linked to insulin resistance and other metabolic dysregulations. Ongoing research continues to explore the therapeutic potential of PKCζ inhibitors with an emphasis on developing agents that specifically target its unique regulatory features without affecting other PKC isoforms (kawano2021activatorsandinhibitors pages 24-25, kawano2022proteinkinasec pages 28-30, silnitsky2023anupdateon pages 19-21).
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