1. Phylogeny  
   Protein kinase C eta (PKCη), encoded by the PRKCH gene and identified by UniProt ID P24723, is classified as a member of the Protein kinase C (PKC) family and more specifically belongs to the novel PKC (nPKC) subfamily that is defined by its diacylglycerol (DAG)‐dependent but Ca²⁺‐independent activation mechanism (basu2019theenigmaticprotein pages 1-4, altman2016proteinkinasec pages 3-4). Orthologs of PKCη are conserved across various mammalian species, consistent with the evolutionary conservation observed within the AGC kinase superfamily and the broader human kinome, which originated in early eukaryotic life (kofler2002moleculargeneticsand pages 3-4, mochlyrosen2012proteinkinasec pages 1-2). Comparative analyses have revealed that although PKCη shares high sequence similarity with other novel PKCs, notably PKCε, it possesses unique regulatory domains that confer its distinctive lipid-binding properties (basu2019theenigmaticprotein pages 7-9, parker2021equivocalexplicitand pages 35-38).
2. Reaction Catalyzed  
   PKCη catalyzes the phosphorylation reaction in which a phosphate group is transferred from ATP to a serine or threonine residue on a substrate protein, thereby converting ATP to ADP and resulting in a phosphorylated protein along with the release of a proton; the reaction is represented as: ATP + [protein] → ADP + [protein]-phosphate + H⁺ (webb2000proteinkinasec pages 1-2, mochlyrosen2012proteinkinasec pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of PKCη requires divalent metal ions, with Mg²⁺ serving as an essential cofactor needed for the proper orientation of ATP in the active site and for catalytic phosphate transfer (webb2000proteinkinasec pages 1-2).
4. Substrate Specificity  
   PKCη exhibits a broad substrate specificity that is characteristic of serine/threonine kinases; it phosphorylates serine and threonine residues in protein substrates that often present in sequence contexts enriched in basic and hydrophobic residues near the phosphoacceptor site, although a strict consensus motif has not been definitively established (reyland2009proteinkinasec pages 1-3, basu2019theenigmaticprotein pages 1-4). The structural configuration of its catalytic domain, along with potential docking interactions provided by its regulatory regions, facilitates phosphorylation of substrates involved in key cellular processes such as cell cycle regulation and differentiation (singh2017proteinkinasec pages 1-3).
5. Structure  
   PKCη is organized into an N-terminal regulatory region and a C-terminal catalytic domain, separated by a flexible hinge segment. The regulatory portion contains tandem cysteine-rich C1 domains responsible for binding DAG and phorbol esters, and a C2-like domain that, unlike in conventional PKCs, lacks the Ca²⁺-binding capability. It also includes an autoinhibitory pseudosubstrate segment that occupies the catalytic cleft under basal conditions, thus maintaining the enzyme in an inactive state (basu2019theenigmaticprotein pages 1-4, webb2000proteinkinasec pages 1-2). The catalytic domain houses critical features such as the activation loop, a catalytic loop containing the ATP-binding site, and a hydrophobic motif that are essential for substrate phosphorylation; structural studies have elucidated the three-dimensional arrangement of the PKCη C2 domain and highlighted key phosphorylation sites that regulate its activity (basu2019theenigmaticprotein pages 9-11, newton2018proteinkinaseca pages 1-3). Advanced computational models, including those generated by AlphaFold, confirm that while PKCη shares a conserved fold with the overall AGC kinase family, its regulatory modules exhibit unique adaptations that underpin its lipid responsiveness and cellular localization (igumenova2015dynamicsandmembrane pages 18-20, newton2018proteinkinaseca pages 3-4).
6. Regulation  
   PKCη is regulated by a multifaceted mechanism that includes phosphorylation, lipid cofactor binding, and protein–protein interactions. Key phosphorylation events occur at the activation loop, the turn motif, and the hydrophobic motif within the catalytic domain, thereby “priming” the kinase for full catalytic activity; kinases such as PDK1 are implicated in triggering these modifications (mochlyrosen2012proteinkinasec pages 1-2, newton2018proteinkinaseca pages 22-23). Activation is achieved upon binding of DAG and phosphatidylserine (PS) to its tandem C1 domains, which leads to a conformational change that displaces the autoinhibitory pseudosubstrate segment and exposes the active site. Notably, PKCη exhibits a resistance to translocation and downregulation in response to sustained stimulation with phorbol esters or cholesterol sulfate, a property that distinguishes it from other PKC isoforms (basu2019theenigmaticprotein pages 1-4, mochlyrosen2012proteinkinasec pages 2-4). Additionally, chaperone proteins such as Hsp70 and Hsp90 contribute to the proper folding and stability of PKCη, further modulating its activity in coordination with its subcellular targeting signals (newton2018proteinkinaseca pages 22-23, altman2016proteinkinasec pages 3-4).
7. Function  
   PKCη plays a central role in a variety of cellular processes that are critical for tissue homeostasis and cell signaling. In keratinocytes, PKCη is essential for promoting differentiation; it activates the tyrosine kinase FYN, which then attenuates epidermal growth factor receptor (EGFR) signaling and leads to growth arrest through a mechanism that involves the dephosphorylation of the retinoblastoma protein (Rb) via its association with the cyclin CCNE1–CDK2–CDKN1B complex, thereby enforcing a G1 phase cell cycle arrest (basu2019theenigmaticprotein pages 1-4, basu2019theenigmaticprotein pages 4-5). Furthermore, PKCη contributes to the reorganization of the actin cytoskeleton in keratinocytes by partnering with RALA to trigger actin depolymerization, a process necessary for the morphological changes observed during terminal differentiation (basu2019theenigmaticprotein pages 5-7). In the context of pre-B cell receptor signaling, PKCη functions downstream of the adaptor protein BLNK by up-regulating the transcription factor IRF4, which in turn promotes light chain gene rearrangement essential for B cell development (information section). In addition, PKCη is implicated in oncogenic processes; for example, it is required for the proliferation of glioblastoma cells and plays a role in preventing apoptosis in MCF-7 breast cancer cells, thus contributing to tumor cell survival (basu2019theenigmaticprotein pages 7-9, reyland2009proteinkinasec pages 1-3). PKCη also regulates epithelial tight junction integrity and foam cell formation, highlighting its involvement in maintaining tissue barrier function and lipid homeostasis (information section).
8. Other Comments  
   The unique regulatory properties of PKCη, such as its resistance to downregulation by prolonged phorbol ester stimulation and its distinctive lipid-binding profile, have made it an attractive target for therapeutic intervention in diseases where its activity is aberrant. Despite considerable efforts, the development of isoform-specific inhibitors for PKCη remains challenging due to the structural conservation among PKC isoforms; however, several pan-PKC inhibitors have been evaluated in preclinical models (mochlyrosen2012proteinkinasec pages 1-2, bosco2011finetuningof pages 9-10). Altered expression and activity of PKCη have been associated with various pathological states, including glioblastoma, certain breast cancers, and disorders of epithelial differentiation, suggesting that dysregulation of PKCη may serve as a biomarker for these conditions (basu2019theenigmaticprotein pages 7-9, newton2018proteinkinasec pages 25-28, aquino2023proteinkinasec pages 2-3). Its role in processes such as cell cycle arrest, cytoskeletal reorganization, and signal transduction underscores the potential impact of targeted modulation of PKCη in therapeutic strategies aimed at cancer and diseases related to epithelial dysfunction.
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