## Phylogeny

Protein kinase C eta (PKCη), encoded by PRKCH, is a serine/threonine kinase belonging to the protein kinase C (PKC) family, which is part of the AGC group of kinases (breitkreutz2007proteinkinasec pages 1-2, newton2018proteinkinasec pages 1-3, marrocco2019pkcandpkn pages 1-2). Within the PKC family, PKCη is classified as a novel PKC (nPKC) isoform, a subgroup that also includes PKCδ, PKCε, and PKCθ (breitkreutz2007proteinkinasec pages 1-2, pal2014theuniqueprotein pages 1-2). This classification is based on domain composition and cofactor requirements and aligns with the phylogenetic framework established by Manning et al., 2002 (garciaconcejo2021proteinkinasec pages 1-2, heinisch2018proteinkinasec pages 1-5, basu2019theenigmaticprotein pages 7-9). PKCη shares the greatest homology with PKCε (pal2014theuniqueprotein pages 2-3). Orthologs of PRKCH exist in mouse and rat (littler2006structureofhuman pages 1-2). The human PRKCH gene is located on chromosome 14q22-23, while the mouse ortholog is on chromosome 12 (pal2014theuniqueprotein pages 1-2).

## Reaction Catalyzed

PKCη catalyzes the phosphotransferase reaction, which involves the transfer of the γ-phosphate from ATP to the hydroxyl group of serine or threonine residues on substrate proteins (breitkreutz2007proteinkinasec pages 1-2, newton2018proteinkinasec pages 1-3, pal2014theuniqueprotein pages 2-3). The chemical reaction is:

ATP + a substrate protein → ADP + a phosphoserine/threonine-protein (harper2010diversefunctionsof pages 1-2, silnitsky2023anupdateon pages 3-5).

## Cofactor Requirements

The catalytic activity of PKCη is calcium (Ca2+)-independent (breitkreutz2007proteinkinasec pages 1-2, pal2014theuniqueprotein pages 1-2, newton2018proteinkinasec pages 1-3). Activation requires the second messenger diacylglycerol (DAG) and acidic phospholipids, particularly phosphatidylserine (PS) (breitkreutz2007proteinkinasec pages 1-2, pal2014theuniqueprotein pages 1-2). Like other kinases, Mg2+ is required as a cofactor for its catalytic activity (newton2018proteinkinasec pages 1-3, newton2018proteinkinasec pages 5-6). Cholesterol sulfate and sulfatide have also been identified as specific activators of PKCη (basu2019theenigmaticprotein pages 1-4, pal2014theuniqueprotein pages 1-2).

## Substrate Specificity

The substrate specificity of PRKCH was determined using a positional scanning peptide array (PSPA) that profiled amino acid preferences from positions -5 to +5 relative to the central serine/threonine phosphorylation site (johnson2023anatlasof pages 1-2). PRKCH is categorized within the basophilic kinase cluster (Cluster 1) (johnson2023anatlasof pages 12-18). Its substrate motif is characterized by a preference for basic residues, such as arginine or lysine, near the phosphorylation site (johnson2023anatlasof pages 12-18). Specifically, PRKCH shows strong preferences for arginine residues at positions -3 and -2 relative to the phosphosite (johnson2023anatlasof pages 12-18). Specificity is also driven by strong negative selection against certain charged residues at specific positions within the motif (johnson2023anatlasof pages 1-2).

## Structure

PKCη has a modular structure composed of an N-terminal regulatory domain linked via a hinge region to a C-terminal catalytic domain (newton2018proteinkinasec pages 1-3, pal2014theuniqueprotein pages 1-2).

The **regulatory domain** contains an autoinhibitory pseudosubstrate sequence, tandem C1 domains (C1A and C1B), and a C2 domain (newton2018proteinkinasec pages 3-5, pal2014theuniqueprotein pages 1-2). The pseudosubstrate sequence is highly divergent among PKC isoforms and maintains the kinase in an inactive state by occupying the catalytic site (pal2014theuniqueprotein pages 1-2). The C1 domains bind DAG and phorbol esters (pal2014theuniqueprotein pages 2-3). The C2 domain lacks key aspartic acid residues for Ca2+ binding, rendering it Ca2+-insensitive; its crystal structure has been solved at 1.75 Å resolution (pal2014theuniqueprotein pages 2-3, littler2006structureofhuman pages 1-2).

The **catalytic domain** has a canonical bilobal kinase fold, as shown by the AlphaFold model for human PKCη (littler2006structureofhuman pages 1-2, garciaconcejo2021proteinkinasec pages 1-2). The smaller N-lobe contains the C-helix, which is critical for ATP positioning and catalysis (littler2006structureofhuman pages 1-2). The larger C-lobe contains the catalytic loop, which harbors residues for phosphoryl transfer, and the activation loop, which is essential for regulating kinase activity and substrate access (littler2006structureofhuman pages 1-2, garciaconcejo2021proteinkinasec pages 1-2, basu2019theenigmaticprotein pages 7-9).

## Regulation

PKCη activity is regulated by post-translational modifications, allosteric mechanisms, and translational control.

* **Phosphorylation**: Activation and maturation of PKCη require priming phosphorylations at three conserved sites: Thr-513 in the activation loop, Thr-655 in the turn motif, and Ser-674 in the hydrophobic motif (pal2014theuniqueprotein pages 2-3, silnitsky2023anupdateon pages 5-7). The activation loop phosphorylation is mediated by PDK-1, while mTORC2 is involved in hydrophobic motif phosphorylation (silnitsky2023anupdateon pages 5-7). Autophosphorylation also occurs, with Ser-28 and Ser-32 in the C2 domain identified as autophosphorylation sites possibly involved in lipid regulation (littler2006structureofhuman pages 1-2). PKCη levels can also be upregulated via transphosphorylation by PKCε (pal2014theuniqueprotein pages 1-2).
* **Allosteric and Conformational Regulation**: In its basal state, PKCη is autoinhibited by its pseudosubstrate sequence (pal2014theuniqueprotein pages 2-3). Binding of DAG to the C1 domains induces a conformational change that displaces the pseudosubstrate, relieving autoinhibition and allowing substrate access (silnitsky2023anupdateon pages 7-9). A unique regulatory feature is its resistance to downregulation following prolonged treatment with phorbol esters (basu2019theenigmaticprotein pages 1-4, pal2014theuniqueprotein pages 1-2).
* **Translational Regulation**: The 5’-UTR of the PRKCH mRNA is long and GC-rich and contains upstream open reading frames, which allows for increased translation under conditions like amino acid starvation (pal2014theuniqueprotein pages 2-3).

## Function

* **Expression and Localization**: PKCη is predominantly expressed in epithelial tissues such as the lung, skin, and heart, as well as the epithelia of the respiratory and digestive tracts (basu2019theenigmaticprotein pages 1-4, pal2014theuniqueprotein pages 1-2). It is also highly expressed in brain microglia but has low overall expression in the brain (gauron2025proteinkinasec pages 10-12, basu2019theenigmaticprotein pages 1-4). Intracellularly, it localizes to the Golgi apparatus, endoplasmic reticulum, nuclear envelope, and plasma membrane (pal2014theuniqueprotein pages 2-3, gauron2025proteinkinasec pages 1-4).
* **Upstream/Downstream Kinases, Substrates and Interacting Partners**: In microglia, PKCη functions downstream of phospholipase C γ (PLCG2) (gauron2025proteinkinasec pages 10-12). It participates in signaling cascades involving Akt, mTOR, Raf/MEK/ERK, JNK/c-Jun, and NF-κB (basu2019theenigmaticprotein pages 4-5). It forms a complex with cyclin E/Cdk2/p21, phosphorylating p21 at Ser146 and modulating Cdk2 activity (basu2019theenigmaticprotein pages 1-4). Other downstream substrates and interacting partners include transglutaminase 1, Fyn kinase, the small G protein RalA, and the anti-apoptotic protein Mcl-1 (basu2019theenigmaticprotein pages 4-5, basu2019theenigmaticprotein pages 5-7). In its Golgi-localized state, its interactome includes protein kinase D (PKD), GOLGA5, and Sec22B (gauron2025proteinkinasec pages 10-12).
* **Cellular Roles**: PKCη has context-dependent functions in proliferation, differentiation, apoptosis, and senescence (basu2019theenigmaticprotein pages 1-4). It promotes the terminal differentiation of keratinocytes but can promote proliferation in other cells like glioblastoma and breast cancer cells (basu2019theenigmaticprotein pages 4-5, basu2019theenigmaticprotein pages 1-4). It exerts anti-apoptotic effects by suppressing caspase activity and upregulating survival proteins like Mcl-1 (basu2019theenigmaticprotein pages 5-7).

## Inhibitors

No specific pharmacological inhibitors for PKCη are detailed in the provided context (basu2019theenigmaticprotein pages 1-4). Experimental inhibition has been reported using the broad-spectrum PKC inhibitor bisindolylmaleimide II, peptide inhibitors, and genetic knockdown via siRNA, shRNA, or antisense oligonucleotides (basu2019theenigmaticprotein pages 4-5, basu2019theenigmaticprotein pages 5-7). The broad PKC inhibitor Gö6983 has also been used experimentally to abolish its kinase function (gauron2025proteinkinasec pages 7-10).

## Other Comments

* **Disease Associations**: PKCη is implicated in multiple cancers, where it can act as either a tumor promoter (glioblastoma, renal cell carcinoma, breast cancer) or a suppressor (hepatocellular carcinoma), depending on the context (basu2019theenigmaticprotein pages 7-9). Its upregulation is associated with chemoresistance in several cancers, including chronic myeloid leukemia and breast cancer (basu2019theenigmaticprotein pages 5-7). An intronic variant (rs7161410) in PRKCH is strongly associated with Alzheimer’s disease (AD) risk under a recessive inheritance model (gauron2025proteinkinasec pages 4-7).
* **Disease Mutations**: Several missense mutations in PRKCH (A19V, K65R, R149Q, V374I, A410S) are linked to AD (gauron2025proteinkinasec pages 7-10). The K65R mutation, located in a surface-exposed region of the C2 domain, enhances PKCη’s localization and signaling at the Golgi apparatus without altering its intrinsic kinase activity (gauron2025proteinkinasec pages 7-10, gauron2025proteinkinasec pages 4-7). The V374I mutation has also been associated with stroke (gauron2025proteinkinasec pages 10-12).

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