## Phylogeny

Protein kinase C alpha (PKCα) is one of the conventional (cPKC) isozymes encoded by the PRKCA gene. The PKC family forms a subgroup within the AGC super-family of Ser/Thr kinases and is evolutionarily related to Akt, p70 S6K and PDK1 (Newton, 2018; Singh et al., 2017). All PKCs trace back to the single yeast kinase Pkc1, and PRKCA orthologues occur throughout metazoans as well as in lower eukaryotes such as Drosophila and Caenorhabditis elegans, indicating strong conservation (Newton, 2003; Unknown authors, 2019).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr ⇌ ADP + phospho-[protein]-L-Ser/Thr (Singh et al., 2017; Unknown authors, 2019).

## Cofactor Requirements

• Ca²⁺, diacylglycerol (DAG) and phosphatidylserine for allosteric activation (Newton, 2010; Silnitsky et al., 2023).  
• Mg²⁺ for ATP binding and catalysis (Newton, 2018; Singh et al., 2017).

## Substrate Specificity

PKCα is a basophilic kinase that prefers basic residues N-terminal to the phospho-site and hydrophobic residues C-terminally. The consensus motif is often written as [R/K]-X-[S/T]-X, with a strong requirement for Lys/Arg at P-3 and a hydrophobic residue at P + 1 (Johnson et al., 2023; Newton, 2018).

## Structure

PKCα is composed of an N-terminal regulatory segment (~35 kDa) joined by a flexible V3 hinge to a C-terminal catalytic domain (~45 kDa) (Newton, 2018; Singh et al., 2017).  
• Regulatory region: autoinhibitory pseudosubstrate, tandem C1A/C1B domains (DAG/phorbol-ester binding) and a Ca²⁺-sensing C2 domain that also contacts anionic phospholipids (Newton, 2010; Ron & Kazanietz, 1999).  
• Catalytic region: canonical AGC kinase fold containing the ATP-binding (C3) and substrate-binding (C4) lobes, a conserved C-helix, hydrophobic spine and a phosphorylation-dependent activation loop (Altman & Kong, 2016; Newton, 2018).

## Regulation

PKCα is kept inactive by its pseudosubstrate occupying the active site. Activation proceeds via:  
1. Membrane recruitment and pseudosubstrate release upon Ca²⁺ binding to the C2 domain and DAG binding to the C1 domain (Newton, 2010; Igumenova, 2015).  
2. Ordered phosphorylation cascade assisted by Hsp90/Cdc37 (Newton, 2018; Singh et al., 2017):  
 • Thr497 in the activation loop by PDK1  
 • Thr638 in the turn motif by mTORC2  
 • Ser657 in the hydrophobic motif by autophosphorylation  
Prolonged activation triggers dephosphorylation by PHLPP phosphatases followed by proteolytic degradation (Unknown authors, 2019).

## Function

PKCα transduces signals that regulate proliferation, apoptosis, migration and differentiation (Singh et al., 2017; Unknown authors, 2019).  
• Expression: widely expressed, with high levels in neurons and glia of the hippocampus and cerebral cortex (Unknown authors, 2019).  
• Upstream signalling: activated downstream of Gq-coupled receptors via PLC-generated DAG and Ca²⁺ (Newton, 2018).  
• Downstream targets: RAF1 (activating MAPK/ERK), K-Ras (negative regulation) and MARCKS (controls PIP2 and actin dynamics) (Unknown authors, 2019).  
• Interacting partners: RACK scaffold proteins, and PDZ-domain proteins such as PICK1 and DLG1 via a C-terminal PDZ ligand (Singh et al., 2017; Unknown authors, 2019).

## Inhibitors

• Activators: phorbol esters (PMA, PDBu), DAG analogues (DiC8) and bryostatin-1 (Newton, 2010; Unknown authors, 2018).  
• Inhibitors: bisindolylmaleimides Gö6976 (cPKC-selective), Gö6983 (broad PKC), Bisindolylmaleimide IV (scaffold-bound PKCα), and ATP-competitive inhibitors midostaurin and riluzole (Newton, 2018; Silnitsky et al., 2023).

## Other Comments

PKCα dysregulation is disease-context dependent. Loss-of-function mutations often occur in cancers, supporting a tumour-suppressive role, whereas germline gain-of-function variants (e.g., M489V) enhance activity and are linked to Alzheimer’s disease (Newton, 2018; Unknown authors, 2019). Additional associations include cardiac hypertrophy, diabetic complications and hypertension (Igumenova, 2015; Silnitsky et al., 2023).

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