## Phylogeny

Protein Kinase C Epsilon (PRKCE) is classified within the AGC kinase family as a novel PKC (nPKC) isoform (manning2002theproteinkinase pages 3-4, manning2002theproteinkinase pages 7-8, zeng2012thebiologyof pages 639-642). It belongs to the eukaryotic protein kinase (ePK) group and is part of a kinase family shared across metazoans (manning2002theproteinkinase pages 3-4). Hierarchical clustering based on amino acid motif selectivity positions PRKCE within the PKC group alongside other isoforms such as PKCA, PKCB, PKCD, and PKCZ (johnson2023anatlasof pages 4-5).

## Reaction Catalyzed

PRKCE catalyzes the phosphorylation reaction involving the transfer of a phosphate group from ATP to a protein substrate: ATP + [a protein] = ADP + [a phosphoprotein] (duquesnes2011pkcdeltaandpkcepsilon pages 4-5, parker2020acancerassociatedgenome pages 1-3, zeng2012thebiologyof pages 639-642).

## Cofactor Requirements

The kinase activity of PRKCE is dependent on Mg2+ as a cofactor but is calcium-independent (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3, scruggs2016prkcegeneencoding pages 1-6).

## Substrate Specificity

Based on a comprehensive analysis of the human serine/threonine kinome, PRKCE is classified as a basophilic kinase with a consensus motif characterized by a strong preference for basic residues, specifically arginine (R) or lysine (K), at positions -3 and/or -2 relative to the phosphoacceptor serine/threonine (S/T) (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 3-4). These consensus motifs include sequences such as R-x-x-S/T and R-x-S/T (johnson2023anatlasof pages 12-18). One source contradicts this, stating a preference for negatively charged or polar residues like Aspartate or Glutamate at the -3 position (scruggs2016prkcegeneencoding pages 1-6).

Information regarding the residue at the +1 position is contradictory across sources. One source indicates a preference for a hydrophobic residue (duquesnes2011pkcdeltaandpkcepsilon pages 4-4), specifically Leu, Ile, Val, or Phe (scruggs2016prkcegeneencoding pages 1-6, scruggs2016prkcegeneencoding pages 12-15). Other sources report a preference for proline (duquesnes2011pkcdeltaandpkcepsilon pages 4-5), a basic residue (unknownauthors2012vhhactivatorsand pages 20-23, zeng2012thebiologyof pages 639-642), or small or hydrophobic residues (zeng2012thebiologyof pages 642-645).

## Structure

PRKCE is composed of an N-terminal regulatory domain and a C-terminal catalytic kinase domain (parker2020acancerassociatedgenome pages 1-3, manning2002theproteinkinase pages 3-4). The regulatory domain contains a pseudosubstrate segment that binds to the catalytic site to maintain autoinhibition, C1 domains that bind diacylglycerol (DAG), and a Ca2+-insensitive C2 domain (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3). The kinase domain features canonical structural elements essential for catalysis, including an activation loop, a C-helix, and a hydrophobic spine that stabilizes the active kinase conformation (parker2020acancerassociatedgenome pages 1-3, scruggs2016prkcegeneencoding pages 1-6, zeng2012thebiologyof pages 639-642).

## Regulation

PRKCE is regulated through allosteric mechanisms and post-translational modification. Activation is triggered by diacylglycerol (DAG) binding to the C1 domain, which induces the release of the autoinhibitory pseudosubstrate segment from the substrate-binding pocket (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3, scruggs2016prkcegeneencoding pages 1-6). Full catalytic activity and stability require phosphorylation by the upstream kinase PDK1 (3-Phosphoinositide-dependent kinase-1) at two key sites: Threonine 566 (T566) within the activation loop and Serine 729 (S729) in the C-terminal hydrophobic motif (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3, scruggs2016prkcegeneencoding pages 1-6).

## Function

PRKCE is expressed in various tissues, including cardiac, neuronal, and immune cells (manning2002theproteinkinase pages 7-8). It operates downstream of the kinase PDK1 and phosphorylates substrates such as MARCKS (myristoylated alanine-rich C kinase substrate), vimentin, and keratin 8 (KRT8) (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3, zeng2012thebiologyof pages 639-642). By targeting these substrates, PRKCE plays roles in regulating the cytoskeleton, cell adhesion, and signaling pathways like the MAPK and NF-κB cascades (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, manning2002theproteinkinase pages 3-4, zeng2012thebiologyof pages 645-648).

## Inhibitors

Known modulators of PRKCE include Bryostatin 1, a DAG analogue, and εV1-2, a peptide inhibitor derived from the V1 domain that selectively inhibits PKCε by blocking its translocation and function (duquesnes2011pkcdeltaandpkcepsilon pages 4-4, parker2020acancerassociatedgenome pages 1-3, scruggs2016prkcegeneencoding pages 1-6).

## Other Comments

PRKCE has been associated with cancer, cardiovascular disease, and inflammatory disorders (manning2002theproteinkinase pages 3-4, manning2002theproteinkinase pages 7-8). The PRKCE gene is located on a chromosomal region that is frequently amplified in tumors (manning2002theproteinkinase pages 3-4).

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