## Phylogeny

Protein kinase C ε (PRKCE) is a member of the AGC kinase family, classified as a novel PKC (nPKC) isoform within the eukaryotic protein kinase (ePK) group and conserved across metazoans (Manning et al., 2002, pp. 3-4, 7-8). Motif-based clustering places PRKCE in the PKC branch together with PKCα/β/δ/ζ isoforms (Johnson et al., 2023, pp. 4-5).

## Reaction Catalyzed

ATP + [a protein] ⇌ ADP + [a phosphoprotein] (Duquesnes et al., 2011, pp. 4-5; Parker et al., 2020, pp. 1-3; Zeng et al., 2012, pp. 639-642).

## Cofactor Requirements

Mg²⁺-dependent and Ca²⁺-independent kinase activity (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3; Scruggs et al., 2016, pp. 1-6).

## Substrate Specificity

Comprehensive peptide-array profiling categorises PRKCE as a basophilic Ser/Thr kinase preferring Arg/Lys at −3 and/or −2 (consensus R-x-x-S/T or R-x-S/T) (Johnson et al., 2023, pp. 3-4, 12-18). One report instead favours Asp/Glu at −3 (Scruggs et al., 2016, pp. 1-6). Preferences for the +1 position are inconsistent: hydrophobic (Leu/Ile/Val/Phe) (Scruggs et al., 2016, pp. 12-15), Pro (Duquesnes et al., 2011, p. 5), basic (Unknown authors, 2012, pp. 20-23; Zeng et al., 2012, pp. 639-642) or generally small/hydrophobic residues (Zeng et al., 2012, pp. 642-645).

## Structure

The protein comprises an N-terminal regulatory region and a C-terminal catalytic domain (Parker et al., 2020, pp. 1-3; Manning et al., 2002, pp. 3-4).  
• Regulatory domain: pseudosubstrate segment (autoinhibition), tandem C1 motifs (DAG binding) and a Ca²⁺-insensitive C2 domain (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3).  
• Catalytic domain: canonical kinase fold with activation loop, C-helix and hydrophobic spine stabilising the active conformation (Parker et al., 2020, pp. 1-3; Scruggs et al., 2016, pp. 1-6; Zeng et al., 2012, pp. 639-642).

## Regulation

1. Allosteric activation: DAG binding to C1 domains releases the autoinhibitory pseudosubstrate, enabling substrate access (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3; Scruggs et al., 2016, pp. 1-6).
2. Phosphorylation: PDK1 phosphorylates T566 in the activation loop and S729 in the C-terminal hydrophobic motif to confer full activity and stability (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3; Scruggs et al., 2016, pp. 1-6).

## Function

PRKCE is expressed in cardiac, neuronal and immune tissues (Manning et al., 2002, pp. 7-8). Acting downstream of PDK1, it phosphorylates MARCKS, vimentin and keratin-8, thereby modulating cytoskeletal organisation, cell adhesion and signalling pathways such as MAPK and NF-κB (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3; Zeng et al., 2012, pp. 639-648).

## Inhibitors

Bryostatin 1 (DAG analogue) and the εV1-2 peptide selectively oppose PKCε activation/translocation (Duquesnes et al., 2011, p. 4; Parker et al., 2020, pp. 1-3; Scruggs et al., 2016, pp. 1-6).

## Other Comments

Genetic amplification and dysregulated PRKCE activity have been linked to cancer, cardiovascular and inflammatory diseases (Manning et al., 2002, pp. 3-4, 7-8).

## 9. References

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