## Phylogeny

PRKCI encodes protein kinase C iota (PKCι), an AGC-group serine/threonine kinase assigned to the atypical PKC (aPKC) subfamily that is distinguished by Ca²⁺/diacylglycerol independence (messerschmidt2005crystalstructureof pages 1-2).  
Comparative analyses show that aPKCs diverged from conventional and novel PKCs but preserve the canonical bilobal catalytic core of the AGC superfamily (fields2008proteinkinasec pages 1-2).  
PKCι shares 72 % overall and 86 % kinase-domain identity with its paralog PKCζ, defining the ζ/ι node within the PKC branch of the human kinome (parker2014atypicalproteinkinase pages 12-14).  
Orthologs are conserved across vertebrates, including mouse PKCλ/Prkci (parker2014atypicalproteinkinase pages 12-14), rat Prkci (shah2022impactofdeleterious pages 1-2) and zebrafish prkci (uhalte2012invivoconditions pages 1-2).  
Kinome surveys anchored by Manning et al. place PRKCI in the PKCι/ζ clade of the AGC group (garciaconcejo2021proteinkinasec pages 1-2).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇄ ADP + [protein]-O-phospho-Ser/Thr (messerschmidt2005crystalstructureof pages 11-13).

## Cofactor Requirements

Catalysis requires Mg²⁺ as the divalent cation (uhalte2012invivoconditions pages 1-2) and is independent of Ca²⁺, diacylglycerol and phosphatidylserine (messerschmidt2005crystalstructureof pages 1-2).

## Substrate Specificity

Proteome-scale mapping assigns PKCι a preference for basic residues (Arg/Lys) at positions P-5 to P-3 preceding the phosphoacceptor Ser/Thr, often followed by a hydrophobic residue at +1 (garciaconcejo2021proteinkinasec pages 1-2).  
Structure-guided modelling with the peptide FKRQGSFF corroborates optimal contacts with Lys/Arg at −3/−2 and a bulky hydrophobe at +1 (messerschmidt2005crystalstructureof pages 11-13).

## Structure

Domain organisation: PB1 (aa 2–108) mediates front-to-back dimerisation with OPCA-motif partners and contains the reactive Cys69 (fields2008proteinkinasec pages 6-8); a single C1 zinc-finger (aa 123–192) binds phosphatidylserine but not phorbol esters (messerschmidt2005crystalstructureof pages 1-2); the kinase domain (aa 254–578) adopts the AGC bilobal fold; the C-terminal AGC extension (aa 523–596) includes the NFD motif and hydrophobic motif analogue (shah2022impactofdeleterious pages 1-2).  
Crystal structures of the catalytic domain with bis-indolyl-maleimide-1 (PDB 1ZRZ, 3.0 Å) reveal an intermediate-open ATP pocket (messerschmidt2005crystalstructureof pages 1-2).  
ATP-bound (PDB 3A8W) and apo (PDB 3A8X) forms resolve C-tail residues 533–551 that buttress ATP binding (takimura2010structuresofthe pages 1-2).  
Key regulatory features include phospho-Thr403 in the activation loop, phospho-Thr555 in the turn motif and a phosphomimetic Glu574 at the hydrophobic motif position that stabilise the active conformation (messerschmidt2005crystalstructureof pages 1-2).  
Displacement of Phe543 within the NFD motif underlies binding of the selective thieno[2,3-d]pyrimidine inhibitor CRT0066854 (parker2014atypicalproteinkinase pages 12-14).

## Regulation

Priming phosphorylation at Thr403 is supplied by PDK1 (parker2014atypicalproteinkinase pages 7-8).  
Autophosphorylation on Thr555 locks the C-tail and maintains activity (messerschmidt2005crystalstructureof pages 1-2).  
mTORC2 signalling preserves the mature, phosphorylated state of PKCι (newton2018proteinkinaseca pages 25-28).  
Src phosphorylates Tyr256, Tyr271 and Tyr325, enhancing nuclear import and survival signalling (parker2014atypicalproteinkinase pages 2-4).  
Activation is additionally controlled by PB1-mediated assembly with Par6, Par3 and p62 scaffolds that relieve pseudosubstrate inhibition (parker2014atypicalproteinkinase pages 4-5).  
Electrophilic gold(I) compounds covalently modify Cys69, blocking Par6 engagement and downstream signalling (fields2008proteinkinasec pages 6-8).  
No experimentally verified ubiquitination or SUMOylation events are reported in the cited literature (messerschmidt2005crystalstructureof pages 14-14).

## Function

PRKCI lies within the 3q26 amplicon; copy-number gain drives over-expression in lung, ovarian, esophageal and pancreatic cancers (parker2014atypicalproteinkinase pages 4-5).  
PKCι is required for Kras-driven transformation; the PKCι–Par6–Rac1 axis disrupts apico-basal polarity and promotes proliferation and invasion (fields2008proteinkinasec pages 6-8).  
In Bcr-Abl-positive leukemia and non-small-cell lung cancer, PKCι engages p62/IKK complexes to activate NF-κB and confer chemoresistance (parker2014atypicalproteinkinase pages 7-8).  
Downstream of PI3K–PDK1, PKCι phosphorylates and inhibits the pro-apoptotic protein BAD, supporting glioblastoma and leukemia cell survival (parker2014atypicalproteinkinase pages 7-8).  
A tri-protein complex of PKCι, Par6A and ECT2 in NSCLC enables PKCι-dependent phosphorylation of ECT2, driving anchorage-independent growth and invasion (parker2014atypicalproteinkinase pages 7-8).

## Inhibitors

Gold(I) thiolate drugs aurothiomalate and aurothioglucose form adducts with Cys69 and disrupt PKCι–Par6 binding (fields2008proteinkinasec pages 6-8).  
Bis-indolyl-maleimide-1 occupies the ATP site as seen in crystal structure 1ZRZ (messerschmidt2005crystalstructureof pages 1-2).  
The thieno[2,3-d]pyrimidine CRT0066854 is an ATP-competitive inhibitor that locks the kinase in an inactive conformation by displacing Phe543 (parker2014atypicalproteinkinase pages 12-14).  
Myristoylated pseudosubstrate peptides provide substrate-competitive inhibition albeit with limited isoform selectivity (parker2014atypicalproteinkinase pages 11-12).

## Other Comments

PKCι is designated a bona fide human oncogene, and elevated expression correlates with poor prognosis across multiple tumour types (fields2008proteinkinasec pages 1-2, parker2014atypicalproteinkinase pages 5-7).  
Mutation of Cys69 to Ser confers resistance to gold-based PB1 inhibitors by preventing covalent adduct formation (fields2008proteinkinasec pages 6-8).  
Tumour-derived kinase-domain mutations E423D (APE motif) and R471C produce altered catalytic properties and substrate selectivity (newton2018proteinkinaseca pages 17-21).

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