## Phylogeny

• Kinome placement: AGC kinase group → Protein kinase C family → novel PKC (nPKC) sub-family (reyland2009proteinkinasec pages 1-3, benes2005thec2domain pages 10-10).  
• Closest paralog: the PKCδ C2 domain shares ≈70 % identity with that of PKCθ, but only ≈45 % with other nPKCs, indicating tight evolutionary linkage between PKCδ and PKCθ (benes2005thec2domain pages 7-8).  
• Experimentally documented orthologs  
– Homo sapiens (PRKCD) (kikkawa2002proteinkinasecδ pages 1-1)  
– Mus musculus (Prkcd) (kikkawa2002proteinkinasecδ pages 1-1)  
– Rattus norvegicus (Prkcd) (kikkawa2002proteinkinasecδ pages 1-1)  
– Danio rerio (prkcd) (reyland2009proteinkinasec pages 1-3)  
– Drosophila melanogaster novel-PKC isoform with PKCδ-like features (harper2010diversefunctionsof pages 1-2)  
– Caenorhabditis elegans PKC-like kinase representing mammalian novel PKCs (reyland2009proteinkinasec pages 1-3)  
– Saccharomyces cerevisiae Pkc1, a distant AGC kinase homolog (harper2010diversefunctionsof pages 1-2)

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-phosphate (kikkawa2002proteinkinasecδ pages 1-2).

## Cofactor Requirements

Catalytic activity strictly requires Mg²⁺; Mn²⁺ can substitute with lower efficacy (unknownauthors2025sixmemberednitrogencontainingheterocycles pages 76-78).

## Substrate Specificity

• Catalytic Ser/Thr phosphorylation: prefers basic PKC consensus motifs, e.g. R/K-X-X-S*/T* or R/K-X-S*/T* (kikkawa2002proteinkinasecδ pages 1-2, steinberg2004distinctiveactivationmechanisms pages 1-2).  
• Regulatory phosphotyrosine recognition: the C2 domain binds Φ/YXXpYΦ sequences enriched in hydrophobic or aromatic residues at –3, –2, –1 and +2, +3 relative to pY (benes2005thec2domain pages 2-3).

## Structure

• Domain organisation: N-terminal pseudosubstrate, tandem C1A/C1B zinc-finger modules (DAG/phorbol binding), non-Ca²⁺-binding C2-like domain, V3 hinge, C-terminal catalytic C3/C4 core and V5 tail (kikkawa2002proteinkinasecδ pages 1-2, harper2010diversefunctionsof pages 1-2).  
• 3-D data  
– Kinase domain crystal structure PDB 3A8W defines active site, C-helix and activation loop (harper2010diversefunctionsof pages 1-2).  
– C2 domain–phosphotyrosine peptide complex PDB 1YRK reveals dedicated pY pocket (benes2005thec2domain pages 10-10).  
– AlphaFold model supplies full-length architecture including flexible hinge (yang2019theroleof pages 3-5).  
• Key catalytic/regulatory residues: Thr505 (activation loop), Ser643 (turn motif), Ser662 (hydrophobic motif) (yang2019theroleof pages 3-5).  
• Unique feature: Glu500 structurally substitutes for phospho-Thr505, explaining partial independence from activation-loop phosphorylation (steinberg2004distinctiveactivationmechanisms pages 3-4).

## Regulation

• Canonical activation: DAG/PS binding to C1B drives membrane translocation and release of the pseudosubstrate (kikkawa2002proteinkinasecδ pages 1-2).  
• Maturation phosphorylations: Thr505, Ser643 and Ser662 installed by PDK1 or autophosphorylation establish catalytic competence (yang2019theroleof pages 3-5).  
• Tyrosine phosphorylation cascade: Abl phosphorylates Y155, enabling Src-mediated Y64; additional sites Y52, Y187, Y311, Y332 and Y512 tune localisation and substrate access (yang2019theroleof pages 5-7, reyland2016multifunctionalrolesof pages 31-33).  
• Proteolytic control: caspase-3 cleavage within the V3 hinge yields a constitutively active nuclear fragment (reyland2016multifunctionalrolesof pages 31-33).  
• Scaffold-directed targeting: RACKs, AKAPs, C-KIPs, p23/Tmp21 and Annexin V govern sub-cellular localisation (reyland2016multifunctionalrolesof pages 4-6).

## Function

• Expression: ubiquitous, with high levels in immune cells and platelets (kikkawa2002proteinkinasecδ pages 1-1, harper2010diversefunctionsof pages 1-2).  
• DNA-damage apoptosis: nuclear PKCδ up-regulates BCLAF1-mediated p53 transcription (reyland2016multifunctionalrolesof pages 1-2).  
• Immune tolerance: restrains B-cell proliferation; loss causes lupus-like autoimmunity (reyland2016multifunctionalrolesof pages 4-6).  
• Inflammation/sepsis: controls NF-κB signalling, neutrophil–endothelial adhesion and vascular permeability (yang2019theroleof pages 7-9).  
• Mitochondrial dynamics & ROS: phosphorylates Drp1 and regulates NADPH oxidase activity (yang2019theroleof pages 13-15).  
• Platelet biology: modulates granule secretion and cytoskeletal rearrangement (harper2010diversefunctionsof pages 1-2).  
• Documented substrates include caspase-3, p52Shc/p66Shc, PMCA, HSP25, BAD and Drp1 (yang2019theroleof pages 5-7).  
• Upstream regulators: DAG/PS, PDK1, Abl and Src family kinases (reyland2009proteinkinasec pages 1-3, reyland2016multifunctionalrolesof pages 31-33).

## Inhibitors

• δV1-1 peptide (SFNSYELGSL-TAT) blocks RACK docking and translocation (yang2019theroleof pages 7-9).  
• ψδ-RACK peptide disrupts intramolecular inhibitory contacts, activating PKCδ (reyland2016multifunctionalrolesof pages 14-15).  
• Rottlerin acts as a non-specific mitochondrial uncoupler that indirectly suppresses PKCδ activity (steinberg2004distinctiveactivationmechanisms pages 8-9).  
• CGP53353 is a competitive ATP-site inhibitor reported to prefer PKCδ (steinberg2004distinctiveactivationmechanisms pages 8-9).

## Other Comments

• Dual oncogenic context: pro-apoptotic after genotoxic stress yet tumor-promoting in Her2⁺ breast and lung cancers (reyland2016multifunctionalrolesof pages 1-2).  
• Pathological over-activation contributes to organ injury in sepsis and ischemia-reperfusion models (yang2019theroleof pages 7-9).

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