## Phylogeny

Orthologs of PKCθ (PRKCQ) are documented in human, mouse, rat and zebrafish, whereas no direct orthologs exist in Drosophila melanogaster, Caenorhabditis elegans or Saccharomyces cerevisiae, indicating a vertebrate-restricted emergence after early whole-genome duplications (garciaconcejo2021proteinkinasec pages 5-7).  
Within the eukaryotic kinome PKCθ resides in the AGC group, PKC family, novel PKC (nPKC) sub-family, forming a δ/θ lineage distinct from the ε/η branch of nPKCs (garciaconcejo2021proteinkinasec pages 1-2, garciaconcejo2021proteinkinasec pages 7-10).

## Reaction Catalyzed

ATP + protein Ser/Thr → ADP + protein Ser/Thr-phosphate (liu2002phosphorylationofthe pages 10-11).

## Cofactor Requirements

Catalysis requires a divalent cation, typically Mg²⁺, coordinated by the conserved magnesium-positioning loop of the kinase core (messerschmidt2005crystalstructureof pages 2-5).

## Substrate Specificity

Biochemical and phosphoproteomic analyses show a preference for basic residues at −3/−2 relative to the phospho-acceptor and a downstream hydrophobic residue, yielding a consensus [R/K]-X-[R/K]-X-S/T-Φ motif (hayashi2007proteinkinasec pages 5-6, liu2002phosphorylationofthe pages 10-11).

## Structure

Domain organisation  
• C2-like domain (N-terminus): Ca²⁺-independent membrane anchor (pappa1998crystalstructureof pages 1-2).  
• Tandem C1A/C1B zinc-finger domains: bind diacylglycerol and phorbol esters; C1B provides high-affinity lipid interaction (rahman2013identificationofthe pages 3-4, czikora2018structuraldeterminantsof pages 1-6).  
• Proline-rich V3 hinge: engages Lck SH3 for CD28-dependent synaptic recruitment (brezar2015pkcthetainregulatory pages 2-4).  
• Bilobed catalytic domain (aa ≈ 361-706) with activation loop Thr538, turn motif Ser676, hydrophobic motif Ser695 and C-terminal V5 tail harbouring a nuclear localisation signal (seco2012allostericregulationof pages 1-2, hagesleiman2015thenovelpkcθ pages 2-3, brezar2015pkcthetainregulatory pages 6-8).

3D structural information  
• C1B domain crystal structure at 1.63 Å (PDB 4FKD) reveals a β-sandwich stabilised by two Zn²⁺ ions; Trp253 projects upward and narrows the activator pocket to 7.6 Å, enhancing membrane affinity (rahman2013identificationofthe pages 6-8).  
• The catalytic domain adopts the canonical AGC fold with an ordered αC-helix, conserved Lys-Glu salt bridge, HRD catalytic triad and DFG motif, as resolved in PKCθ-related structures and confirmed for PKCθ by crystallography (igumenova2015dynamicsandmembrane pages 25-27).  
Key regulatory elements  
Phosphorylated Thr538 lines the activation loop, anchoring Arg/Lys residues that stabilise the active conformation; Ser695 packs against the hydrophobic spine, while the C-terminal tail embraces both lobes to secure the active kinase (seco2012allostericregulationof pages 1-2, hagesleiman2015thenovelpkcθ pages 1-2).  
Unique feature  
The upward orientation of Trp253 in C1B is distinctive to PKCθ among nPKCs and underlies its selective, stable accumulation at the immunological synapse (rahman2013identificationofthe pages 6-8).

## Regulation

Phosphorylation  
• Thr538 (activation loop) – primed by PDK1 for maturation and phosphorylated by GLK/MAP4K3 upon TCR engagement; indispensable for catalytic activity and synaptic localisation (brezar2015pkcthetainregulatory pages 2-4, hayashi2007proteinkinasec pages 5-6).  
• Thr219 – PKCθ autophosphorylation required for central SMAC accumulation (brezar2015pkcthetainregulatory pages 2-4).  
• Ser676 (turn motif) and Ser695 (hydrophobic motif) – cis-autophosphorylation events that stabilise the enzyme (hayashi2007proteinkinasec pages 6-8).  
• Tyr90 (C2-like) and Tyr907 – phosphorylated by Lck; modulate conformation and create potential SH2 docking sites (brezar2015pkcthetainregulatory pages 2-4, hayashi2007proteinkinasec pages 5-6).

Sumoylation  
• Lys325 and Lys506 – conjugated with SUMO1 by PIASxβ; SENP1 removes the modification. Sumoylation augments immunological-synapse targeting, kinase activity and downstream NF-κB, NFAT and AP-1 signalling (wang2015tcrinducedsumoylationof pages 1-5).

Allosteric and conformational control  
DAG binding to C1B displaces the autoregulatory pseudosubstrate and, together with PI3-K/Vav1-dependent membrane recruitment, completes activation (hayashi2007proteinkinasec pages 5-6, rahman2013identificationofthe pages 3-4).

## Function

Expression  
PKCθ is highly expressed in thymocytes and peripheral T lymphocytes with lower levels in other tissues (rahman2013identificationofthe pages 1-3, brezar2015pkcthetainregulatory pages 1-2).

Upstream regulators  
TCR/CD28 costimulation generates DAG and recruits Lck, Vav1, PI3-K and GLK to initiate PKCθ activation (hayashi2007proteinkinasec pages 5-6, brezar2015pkcthetainregulatory pages 2-4).

Direct substrates / interactors  
• CARD11/CARMA1 serine cluster – phosphorylation triggers BCL10-MALT1 recruitment and canonical IKK activation (hayashi2007proteinkinasec pages 4-5).  
• SPAK Ser311 – mediates AP-1 activation (hayashi2007proteinkinasec pages 4-5).  
• WASP-interacting protein Ser488 – promotes actin polymerisation (hayashi2007proteinkinasec pages 6-8).  
• IRS1 Ser1101 – attenuates Akt signalling and links PKCθ to insulin resistance (hayashi2007proteinkinasec pages 6-8).  
• Tec family kinase – sustained association enhances PLCγ1 phosphorylation and Ca²⁺ influx (hayashi2007proteinkinasec pages 4-5).

Pathways  
PKCθ is an obligate node for TCR-induced NF-κB, AP-1, NFAT and JNK activation, thereby governing IL-2 production, T-cell proliferation, survival and Th2/Th17 differentiation (brezar2015pkcthetainregulatory pages 2-4, hayashi2007proteinkinasec pages 4-5).

## Inhibitors

• Sotrastaurin (AEB071) – multi-PKC ATP-competitive inhibitor that suppresses early T-cell activation and has progressed to clinical evaluation (brezar2015pkcthetainregulatory pages 5-6).  
• CGX1079 and CGX0471 – block Thr538 phosphorylation, prevent synaptic translocation and dampen NF-κB/NFAT/AP-1 signalling (brezar2015pkcthetainregulatory pages 6-8).  
• Compound C20 increases regulatory T-cell suppressive capacity, whereas Compound C27 exhibits high selectivity for PKCθ with minimal off-target activity (brezar2015pkcthetainregulatory pages 5-6, brezar2015pkcthetainregulatory pages 6-8).  
• R524 inhibits PKCθ and PKCα, curbing CD4⁺ T-cell proliferation and reducing graft-versus-host disease in models (brezar2015pkcthetainregulatory pages 9-10).

## Other Comments

PKCθ-mediated IRS1 phosphorylation implicates the kinase in metabolic disorders such as insulin resistance (hayashi2007proteinkinasec pages 6-8).  
Sumoylation-dependent regulation of PKCθ influences HIV-1 transcription via effects on NF-κB, providing a link to viral pathogenesis (brezar2015pkcthetainregulatory pages 6-8).  
Pharmacologic dual inhibition of PKCθ and PKCα mitigates graft-versus-host disease while preserving graft-versus-leukaemia effects, highlighting therapeutic potential in transplantation immunology (brezar2015pkcthetainregulatory pages 9-10).

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