## Phylogeny

• Member of the AGC kinase group → protein kinase C (PKC) family → conventional PKC subfamily (cPKC) together with PKCα and PKCγ (garciaconcejo2021proteinkinasec).  
• Whole-genome duplications 1R/2R expanded an ancestral set of five PKC genes to the 12-member vertebrate repertoire that includes PRKCB (garciaconcejo2021proteinkinasec).  
• Orthologs retaining the C1–C2–kinase–V5 architecture are documented in Homo sapiens, Mus musculus, Rattus norvegicus, Bos taurus and Danio rerio (manning2002theproteinkinase, hunter2015theeukaryoticprotein).  
• Presence in invertebrates is disputed: kinome surveys annotate distant PKCβ-like sequences in Drosophila and Caenorhabditis, whereas detailed PKC family analysis reports loss of true orthologs in these taxa (hunter2015theeukaryoticprotein, garciaconcejo2021proteinkinasec).

## Reaction Catalyzed

ATP + protein L-Ser/Thr → ADP + protein phospho-L-Ser/Thr (grodsky2006structureofthe).

## Cofactor Requirements

Catalytic turnover requires Mg²⁺ coordinated to the ATP phosphates; Mn²⁺ can substitute in vitro (grodsky2006structureofthe).

## Substrate Specificity

• Prefers basic residues at −3/−2 relative to the phosphoacceptor serine/threonine; verified consensus for classic PKCs: XRXXSXRX (zerihun2023anupdateon).

## Structure

• Modular organisation: N-terminal pseudosubstrate → C1A → C1B → Ca²⁺-sensing C2 → flexible hinge → bilobal kinase domain → C-terminal V5 tail (newton2018proteinkinasec).  
• 2.6 Å crystal structure of the isolated kinase domain bound to bisindolylmaleimide shows a fully primed conformation; catalytic Lys371–Glu390 salt bridge aligned, activation loop ordered (grodsky2006structureofthe).  
• Regulatory phosphosites: Thr500 (activation loop), Thr641 (turn motif) and Ser660 (hydrophobic motif/R-helix) form an intramolecular network that stabilises the active core (grodsky2006structureofthe).  
• Full-length rat PKCβII structure reveals an autoinhibited “C1B clamp” that blocks both ATP and DAG binding sites (igumenova2015dynamicsandmembrane).  
• Membrane docking involves the C2 domain inserting Ca²⁺-bridged loops containing Trp245/Trp247 into phosphatidylserine/PIP₂ bilayers (igumenova2015dynamicsandmembrane).  
• V5 tail harbours a PXXP motif that recruits Hsp90 and folds against the kinase N-lobe to assist maturation (newton2018proteinkinasec).

## Regulation

• Ordered priming: PDK1 phosphorylates Thr500; autophosphorylation at Thr641 and Ser660 completes maturation and locks the pseudosubstrate into the active site (newton2018proteinkinasec).  
• Activation requires Ca²⁺ binding to the C2 domain and DAG/phorbol-ester binding to C1B, which eject the pseudosubstrate and rotate the C-helix (guo2004proteinkinasec).  
• Ser660 phosphorylation increases Ca²⁺/phosphatidylserine affinity, prolonging membrane residence (igumenova2015dynamicsandmembrane).  
• PHLPP dephosphorylates the hydrophobic motif, triggering ubiquitin-proteasome degradation (newton2018proteinkinasec).  
• Chaperones and scaffolds: Hsp90, Pin1, mTORC2 component Sin1 and RACK1 bind the V5 tail to control folding, localisation and down-regulation (newton2018proteinkinasec, igumenova2015dynamicsandmembrane).  
• Negative feedback: PKCβ phosphorylates Bruton’s tyrosine kinase at Ser180, limiting BTK membrane recruitment after BCR stimulation (guo2004proteinkinasec).

## Function

• High expression in B lymphocytes, vascular endothelial cells, adipocytes and several epithelial tissues (dowling2015targetingproteinkinase).  
• B-cell receptor signalling: directly phosphorylates CARD11 at Ser559/Ser644/Ser652, recruiting BCL10–MALT1–TAK1 to activate canonical NF-κB; essential for B-cell survival (guo2004proteinkinasec).  
• Drives VEGF-dependent endothelial proliferation through Raf–MEK–ERK cascade and retinoblastoma protein phosphorylation; promotes tumour angiogenesis (grodsky2006structureofthe).  
• Metabolic regulation: chronic activation in adipocytes induces mitochondrial dysfunction, oxidative stress, inflammation and systemic insulin resistance via p66Shc (mehta2014proteinkinasecbeta).  
• Exercise down-regulates PKCβ in muscle and liver; PRKCB knockout abolishes the insulin-sensitising effect of exercise (mehta2014proteinkinasecbeta).

## Inhibitors

• Ruboxistaurin (LY333531): macrocyclic bisindolylmaleimide, ATP-competitive; IC₅₀ = 4.7 nM (PKCβ1) and 5.9 nM (PKCβ2) (kawano2021activatorsandinhibitors).  
• Enzastaurin: acyclic bisindolylmaleimide; IC₅₀ ≈ 6 nM for PKCβ, reduced potency toward PKCα/γ/ε (kawano2021activatorsandinhibitors).  
• Bisindolylmaleimide I (BIM-1) defines hinge-binding mode in the PKCβII crystal structure (grodsky2006structureofthe).  
• Midostaurin and other staurosporine derivatives inhibit PKCβ but lack strict isoform selectivity (dowling2015targetingproteinkinase).

## Other Comments

• PKCβ over-activation contributes to diabetic retinopathy, nephropathy and macular oedema; ruboxistaurin reduces vascular leakage and visual loss in experimental models (grodsky2006structureofthe).  
• PRKCB expression is frequently lost in malignant melanocytes and melanoma cell lines, underscoring context-dependent roles in cancer (dowling2015targetingproteinkinase).  
• A functional PRKCB promoter polymorphism correlates with insulin resistance in human cohorts (mehta2014proteinkinasecbeta).