## Phylogeny

• Kinome position: Ca²⁺/calmodulin-dependent protein kinase (CaMK) group, CAMK1/2 branch of the human kinome as mapped by Manning et al. 2002 (by reference within) (byrne2023evolutionaryandcellular pages 17-18).  
• Closest paralog: PSKH2, a catalytically impaired pseudokinase that diverged from PSKH1 yet retains the kinase-fold core (byrne2023evolutionaryandcellular pages 1-3).  
• Additional relatives: CaMK1γ and CaMK2 share conserved catalytic and regulatory motifs with PSKH1 (unknownauthors2024illuminatingtheregulation pages 9-11).  
• Ortholog distribution: PSKH1 orthologs are conserved across vertebrates; PSKH2 is absent from mouse and rat genomes, highlighting differential evolutionary retention (shrestha2020cataloguingthedead pages 13-14).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⟶ ADP + protein-Ser/Thr-P (unknownauthors2024illuminatingtheregulation pages 78-84, unknownauthors2024illuminatingtheregulation pages 131-137).

## Cofactor Requirements

• Mg²⁺ is required for phosphotransfer activity in vitro (unknownauthors2024illuminatingtheregulation pages 78-84).  
• Ca²⁺/calmodulin enhances—but is not essential for—basal catalytic activity, particularly in non-autophosphorylated enzyme preparations (unknownauthors2024illuminatingtheregulation pages 101-108, unknownauthors2024illuminatingtheregulation pages 131-137).

## Substrate Specificity

• Positional-scanning peptide arrays defined a basophilic consensus motif L-x-R-T-x-S\*-F-x-x-x, with strict Arg at –3 and strong Ser over Thr selection as the phospho-acceptor (unknownauthors2024illuminatingtheregulation pages 175-180).  
• Independent profiling confirmed the Arg(–3) preference and overall serine specificity (horne2025pskh1kinaseactivity pages 2-3).

## Structure

• N-terminal segment (residues 1-30): dual lipidation sites Gly2 (N-myristoylation) and Cys3 (palmitoylation) plus a PxxP SH3-binding motif (unknownauthors2024illuminatingtheregulation pages 201-206).  
• Calmodulin-binding domains  
 – N-terminal CBD (~80-100) harboring an inverted 1-5-8 motif; Phe90 anchors CaM (unknownauthors2024illuminatingtheregulation pages 140-144).  
 – C-terminal CBD containing autophospho-Ser372 that modulates CaM affinity (unknownauthors2024illuminatingtheregulation pages 140-144).  
• Catalytic domain (≈86-424): canonical VAIK (Lys104), HRD (Asp218), DFG (Asp254) motifs intact; deletions beyond residue 98 abolish activity (unknownauthors2024illuminatingtheregulation pages 140-144).  
• Activation segment: principal autophosphosite Thr256; adjacent Thr260 and distal Ser363/Ser372 also phosphorylated (unknownauthors2024illuminatingtheregulation pages 101-108, unknownauthors2024illuminatingtheregulation pages 140-144).  
• Quaternary arrangement: AlphaFold2 modelling predicts a head-to-toe homodimer capable of simultaneous CaM engagement at both termini (unknownauthors2024illuminatingtheregulation pages 140-144).  
• No experimentally determined crystal or NMR structure is available; AlphaFold model AF-P11801-F1 provides full-length coordinates (unknownauthors2024illuminatingtheregulation pages 140-144).

## Regulation

Post-translational modifications  
• Cis-autophosphorylation: Thr256, Thr260, Ser363, Ser372—collectively elevate catalytic turnover (unknownauthors2024illuminatingtheregulation pages 101-108, unknownauthors2024illuminatingtheregulation pages 140-144).  
• Lipidation: N-myristoylation at Gly2 and palmitoylation at Cys3 direct membrane and Golgi localisation (unknownauthors2024illuminatingtheregulation pages 201-206).

Allosteric and conformational control  
• Ca²⁺/calmodulin modestly stimulates activity at low Ca²⁺ (unknownauthors2024illuminatingtheregulation pages 131-137).  
• CREC-family Ca²⁺ sensors Reticulocalbin-1 and Reticulocalbin-3 suppress autophosphorylation and catalytic output, whereas calumenin selectively reduces autophosphorylation (unknownauthors2024illuminatingtheregulation pages 131-137).  
• UNC119B binds the kinase domain and enhances activity independently of N-terminal acylation (horne2025pskh1kinaseactivity pages 1-2).  
• Glucose withdrawal increases PSKH1 activity, linking catalytic output to metabolic stress (unknownauthors2024illuminatingtheregulation pages 16-21).

## Function

Expression and localisation  
• Broad tissue expression with pronounced levels in testis; over-expressed in prostate, lung and kidney cancers (horne2025pskh1kinaseactivity pages 1-2, unknownauthors2024illuminatingtheregulation pages 21-24).  
• Localises to Golgi, centrosome, nucleus and, when dually acylated, the plasma membrane (unknownauthors2024illuminatingtheregulation pages 201-206, unknownauthors2024illuminatingtheregulation pages 189-193).

Signalling roles  
• Pre-mRNA splicing regulation through phosphorylation of SR-rich splice factors (unknownauthors2024illuminatingtheregulation pages 16-21).  
• Metabolic sensor that drives fatty-acid utilisation and sustains prostate cancer cell proliferation during glucose scarcity (unknownauthors2024illuminatingtheregulation pages 175-180, unknownauthors2024illuminatingtheregulation pages 189-193).  
• Vesicle trafficking and cell migration via interactions with SORBS1, PAK4 and additional actin-cytoskeleton regulators (unknownauthors2024illuminatingtheregulation pages 210-214).  
• Direct substrate: phosphorylates RSK1 at Ser380, facilitating PDK1-mediated RSK1 activation and downstream inhibition of eEF2K (unknownauthors2024illuminatingtheregulation pages 180-185).  
• Upstream kinase: PAK1 can phosphorylate PSKH1 activation loop Thr256 in vitro (unknownauthors2024illuminatingtheregulation pages 157-163).  
• Protein interaction network includes Golgi resident GOLGA8R and Ca²⁺ sensors such as Reticulocalbin-3 (horne2025pskh1kinaseactivity pages 2-3).

## Inhibitors

• ATP-competitive compound “C2” suppresses PSKH1 activity and blocks proliferation of PSKH1-proficient prostate cancer cells under glucose stress (unknownauthors2024illuminatingtheregulation pages 175-180).  
• Chemoproteomic profiling identified afatinib and neratinib as covalent ligands of PSKH1, although potency data were not reported (shrestha2020cataloguingthedead pages 13-14).

## Other Comments

• Disease associations:  
 – Key driver of metastatic prostate cancer progression via metabolic rewiring (unknownauthors2024illuminatingtheregulation pages 175-180).  
 – Loss-of-function mutations implicated in hepatorenal ciliopathy (horne2025pskh1kinaseactivity pages 1-2).  
 – P66L and R79L variants within the N-terminal PxxP motif linked to inflammatory disorders such as Crohn’s disease (unknownauthors2024illuminatingtheregulation pages 201-206).  
• Experimental limitation: absence of a phospho-Thr256-specific antibody hampers direct monitoring of activation-loop status (unknownauthors2024illuminatingtheregulation pages 157-163).

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