## Phylogeny

Orthologous kinases are documented in Schizosaccharomyces pombe (Prp4p) (gross1997functionalanalysisof pages 1-2), Fusarium graminearum (FgPrp4) (gao2016fgprp4kinaseis pages 1-2), Drosophila melanogaster and Caenorhabditis elegans (gao2013evaluationofcancer pages 1-2).  
Human PRPF4B belongs to the CMGC kinase group and clusters within the DYRK/CLK branch; the catalytic domain shares closest structural similarity to CLK2 and DYRK2 (gao2013evaluationofcancer pages 9-11).  
A conserved insertion encompassing residues 925–971 is present in PRP4-lineage members and absent from other CMGC relatives, delineating a distinct PRP4 sub-clade (gao2013evaluationofcancer pages 11-12).

## Reaction Catalyzed

ATP + protein L-serine/threonine ⇄ ADP + protein O-phospho-L-serine/threonine (gao2013evaluationofcancer pages 7-8, gross1997functionalanalysisof pages 1-2).

## Cofactor Requirements

Catalytic activity is Mg²⁺-dependent in biochemical assays with recombinant human PRPF4B (gao2013evaluationofcancer pages 1-2).

## Substrate Specificity

Phosphoproteomic analysis after inducible knock-down highlighted over-represented motifs XXS*PXX and XXS*XXE\*XX, indicating preference for serine followed by proline or acidic residues (gao2013evaluationofcancer pages 8-9).  
Validated substrates include the RS domain of SRSF1/ASF/SF2 (gross1997functionalanalysisof pages 1-2), U4/U6-U5 tri-snRNP components PRPF6 and PRPF31 (schneider2010humanprp4kinase pages 1-2), Ser104 of PAK4 (gao2013evaluationofcancer pages 7-8), and multiple threonines in the N-terminus of Prp1 (PRPF6 ortholog) (lutzelberger2010thenterminusof pages 8-9).

## Structure

Full-length PRPF4B (1–1007 aa) comprises an N-terminal RS-rich segment (~1–300), a Lys-rich linker (~301–649), and a C-terminal bilobal kinase domain (~650–1007) (gross1997functionalanalysisof pages 1-2).  
Crystal structures of the catalytic domain are available in apo, ADP-, AMPPNP-, and inhibitor-bound states at 2.00–2.44 Å resolution (PDB 4IAN, 4IFC, 4IIR, 4IJP) (gao2013evaluationofcancer pages 11-12).  
Key catalytic elements are Lys717–Glu734, the Asp832-Phe834 DFG motif, and an activation loop containing phospho-Tyr849 (gao2013evaluationofcancer pages 9-11).  
Unique structural features include Pro769 in the hinge and Cys833 immediately N-terminal to the DFG motif; together they create a hydrophobic pocket not conserved in related kinases (gao2013evaluationofcancer pages 12-13).  
Residues 925–971 form a PRP4-specific insert that generates an auxiliary surface groove proposed to contribute to substrate recognition (gao2013evaluationofcancer pages 12-13).  
The glycine-rich loop around Thr693 adopts ligand-dependent open and closed conformations (gao2013evaluationofcancer pages 9-11).  
The AlphaFold model (AF-Q13523-F1) recapitulates the bilobal fold and positions the flexible RS domain peripheral to the kinase core (gao2013evaluationofcancer pages 1-2).

## Regulation

PRPF4B undergoes autophosphorylation (schneider2010humanprp4kinase pages 1-2).  
Phosphorylation of Ser289 in the N-terminal SR-rich region is essential for activity of the FgPrp4 ortholog, suggesting functional conservation (gao2016fgprp4kinaseis pages 2-4).  
The activation loop is observed phosphorylated on Tyr849 in crystal structures, consistent with an active conformation (gao2013evaluationofcancer pages 9-11).  
Physical interaction with CLK1 indicates potential cross-regulatory phosphorylation among spliceosomal kinases (eckert2016prp4kinasegrants pages 19-20).  
HER2 signaling up-regulates PRPF4B transcription, modulating taxane sensitivity in breast and ovarian cancer cells (corkery2015prp4kisa pages 139-144).  
ATP-competitive inhibitor Compound A stabilizes the active conformation of the kinase domain (gao2013evaluationofcancer pages 11-12).

## Function

PRPF4B phosphorylates PRPF6 and PRPF31 during their incorporation into the U4/U6-U5 tri-snRNP, facilitating spliceosome B-complex formation (schneider2010humanprp4kinase pages 1-2).  
Deletion of FgPrp4 reduces splicing efficiency for over 60 % of genes and causes severe growth defects in F. graminearum (gao2016fgprp4kinaseis pages 1-2).  
Inducible knock-down in PANC-1 cells decreases phosphorylation of mRNA-processing factors and spindle-checkpoint proteins, leading to loss of MAD1 at kinetochores and mitotic defects (gao2013evaluationofcancer pages 6-7).  
Genome-wide RNAi/shRNA screens identify PRPF4B as essential for survival of multiple cancer cell lines (gao2013evaluationofcancer pages 1-2).  
Over-expression in HCT116 colon cancer cells inhibits RhoA, dephosphorylates cofilin, reorganizes actin stress fibers, and induces epithelial-mesenchymal transition (islam2018prp4kinaseinduces pages 24-30).  
PRPF4B is broadly expressed in cancer cell lines and is up-regulated by HER2 signaling (gao2013evaluationofcancer pages 1-2, corkery2015prp4kisa pages 139-144).

## Inhibitors

Compound A: biochemical IC₅₀ = 0.016 µM; co-crystal structure 4IJP reveals hydrogen bonds with hinge residues and hydrophobic interactions surrounding Cys833 (gao2013evaluationofcancer pages 11-12).  
The presence of Cys833 adjacent to the DFG motif provides a tractable site for designing irreversible covalent inhibitors (gao2013evaluationofcancer pages 12-13).

## Other Comments

shRNA depletion or pharmacological inhibition of PRPF4B resensitizes chemoresistant ovarian and breast cancer cells to paclitaxel (gao2013evaluationofcancer pages 1-2).  
In retinitis pigmentosa patient lymphoblasts, PRPF4 shows reduced incorporation into tri-snRNPs, implicating spliceosome defects in retinal degeneration (tanackovic2011prpfmutationsare pages 3-4).

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