## Phylogeny

Phosphatidylinositol-5-phosphate 4-kinases (PIP4Ks) are metazoan-specific lipid kinases also found in choanoflagellates but absent from unicellular eukaryotes such as S. cerevisiae (Krishnan et al., 2024; Raghu, 2021). Three vertebrate isoforms (PIP4K2A, PIP4K2B, PIP4K2C) are conserved in worms, flies, zebrafish, mice and humans (Kolay et al., 2016; Krishnan et al., 2024). The family belongs to the phosphoinositide kinase (PIK) superfamily yet is distinct from PI3Ks and PI4Ks (Brown & Auger, 2011).

## Reaction Catalyzed

Phosphatidylinositol-5-phosphate + ATP ⇌ phosphatidylinositol-4,5-bisphosphate + ADP (Krishnan et al., 2024; Sumita et al., 2016).

## Cofactor Requirements

Activity requires a divalent metal ion, typically Mg²⁺ or Mn²⁺, which coordinates the nucleotide triphosphate (Unknown Authors, 2022).

## Substrate Specificity

PIP4K2B is a lipid kinase specific for phosphatidylinositol-5-phosphate (PI5P); specificity is governed by structural elements such as the activation loop, which when swapped with that of a PIP5K alters lipid preference (Krishnan et al., 2024; Raghu, 2021; Unknown Authors, 2020).

## Structure

The human PIP4K2B crystal structure (PDB 3X01) reveals a homodimer formed via N-terminal β-sheets that create a flat, positively charged membrane-binding surface (Unknown Authors, 2020). Heterodimerization with other PIP4K isoforms is also observed (Clarke & Irvine, 2013; Raghu, 2021). Key features include a PI5P-binding pocket, a nucleotide-binding site, and an activation loop; residues Thr201 and Phe205 shape the guanine-specific pocket underlying GTP preference (Sumita et al., 2016).

## Regulation

• Phosphorylation at Ser326 by p38 MAPK diminishes kinase activity (Trempolec et al., 2013).  
• Acetylation of Lys239 by p300 and de-acetylation by SIRT1 modulate function (Unknown Authors, n.d.).  
• Acts as an intracellular GTP sensor; activity scales with physiological GTP levels (Sumita et al., 2016).  
• Catalysis-independent inhibition of PIP5Ks at acidic membranes suppresses PI(4,5)P₂ and downstream PI3K/AKT signalling (Wang et al., 2019; Unknown Authors, 2020).  
• Nuclear localisation, mediated by an intrinsic NLS, permits regulation in the nucleus, plasma membrane and ER (Raghu, 2021; Unknown Authors, 2020).

## Function

Highly expressed in skeletal muscle and present in liver and brain (Unknown Authors, 2020).  
Catalytic activity is required for autophagosome–lysosome fusion (Raghu, 2021).  
In nuclei, controls PI5P levels to influence transcription factors such as ING2, TAF3 and UHRF1 during DNA-damage responses (Raghu, 2021).  
Kinase-independent binding to PIP5Ks attenuates insulin/PI3K/AKT and TORC1 pathways, contributing to metabolic regulation; Pip4k2b-knockout mice display increased insulin sensitivity (Wang et al., 2019; Unknown Authors, 2020).

## Inhibitors

Covalent and non-ATP-competitive allosteric small-molecule inhibitors targeting the PI5P-binding site have been reported, but display micromolar potency and poor isoform selectivity (Jin & Xue, 2023; Unknown Authors, 2020).

## Other Comments

Among mammalian isoforms catalytic efficiency ranks PIP4K2A ≫ PIP4K2B ≫ PIP4K2C (Unknown Authors, 2020; Raghu, 2021). PIP4K2B expression is dysregulated in cancer: transcripts increase in some leukaemias; over-expression can restrict glioblastoma growth, whereas low levels in breast tumours correlate with larger size and poorer prognosis (Raghu, 2021; Unknown Authors, 2014). Combined loss of PIP4K2A/2B slows tumour growth in p53-null mice (Raghu, 2021).

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