## Phylogeny

PIP4K2A belongs to the phosphoinositide kinase (PIK) superfamily, specifically the Type II phosphatidylinositol phosphate kinase subfamily (also termed PIP4K/PIPkinC). It is one of three mammalian isoforms (PIP4K2A, 2B, 2C) and is conserved throughout metazoans, with orthologues detected as far down as insects, but is absent from unicellular eukaryotes (Clarke & Irvine, 2013; Raghu, 2021). Within its catalytic domain, it shares sequence homology with Type I (PIP5K) and Type III (PIKfyve) kinases (Muftuoglu et al., 2016).

## Reaction Catalyzed

ATP + 1-phosphatidyl-1D-myo-inositol 5-phosphate ⇌ ADP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate (Bulley et al., 2016; Raghu, 2021).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Bulley et al., 2016; Clarke & Irvine, 2013).

## Substrate Specificity

Primary substrate is PI5P, which is phosphorylated at the 4-position to yield PI(4,5)P₂ (Bulley et al., 2016). In vitro, the enzyme can also phosphorylate PI3P to PI(3,4)P₂ with much lower efficiency (Muftuoglu et al., 2016). Specificity is governed by the C-terminal activation loop, a specificity loop and a dedicated monophosphate-binding pocket (Muftuoglu et al., 2016; Unknown Authors, 2021).

## Structure

PIP4K2A comprises an N-lobe/C-lobe protein-kinase fold, a dimerisation domain and a unique PIP-binding insertion within the C-lobe (Unknown Authors, 2022). The crystal structure (PDB 2YBX) reveals a homodimer formed via N-terminal β-sheets (Unknown Authors, 2020). A conserved C-terminal activation loop and an intrinsic G-loop contribute to high catalytic activity (Unknown Authors, n.d.; Unknown Authors, 2021). Regions lacking crystallographic data can be modelled with AlphaFold (Unknown Authors, 2020).

## Regulation

Activity is modulated by post-translational modifications (sites not specified) and by signal-dependent localisation changes. PIP4K2A is a substrate of mTORC1, supporting basal mTORC1 signalling during nutrient starvation (Jin & Xue, 2023). Protein-kinase-C-dependent translocation, heterodimer formation with other PIP4K isoforms (notably PIP4K2B), and an N-terminal VMLLPDD motif that negatively regulates PIP5Ks further influence its activity (Bulley et al., 2016; Raghu, 2021; Unknown Authors, n.d.).

## Function

Highly expressed in peripheral blood cells and distributed across cytoplasm, nucleus, peroxisomes, plasma membrane and early endosomes (Fiume et al., 2015; Hu et al., 2018). It interfaces with mTORC1/2, Akt and Class I PI3K signalling pathways (Bulley et al., 2016; Jin & Xue, 2023). Binding partners include PIP4K2B, PIP5Ks and the endosomal factor TOM1 (Raghu, 2021). Cellular roles encompass:  
• Generation of peroxisomal PI(4,5)P₂ to enable lysosome-peroxisome contact sites and cholesterol trafficking (Hu et al., 2018).  
• Control of autophagosome–lysosome fusion and autophagosome biogenesis (Raghu, 2021).  
• Support of B-cell growth/survival and regulation of regulatory-T-cell proliferation and function (Bulley et al., 2016; Jin & Xue, 2023).

## Inhibitors

No selective small-molecule inhibitors are reported in the cited literature. Functional depletion or combined blockade of PIP4Ks with mitotic pathways can induce cancer-selective lethality (Bulley et al., 2016; Raghu, 2021).

## Other Comments

PIP4K2A is essential for proliferation of acute myeloid leukaemia cells and its transcripts are elevated in several leukaemias (Bulley et al., 2016; Raghu, 2021). Loss of the kinase slows tumour growth in p53-null mice, whereas over-expression can suppress glioblastoma growth (Raghu, 2021). Mutations in the wider PIPK family are linked to cancer and diabetes (Muftuoglu et al., 2016). Impaired function may contribute to lysosomal storage disorders through defective cholesterol transport (Hu et al., 2018). Gene deletion causes immune hyper-activation (Jin & Xue, 2023), and polymorphisms have been associated with neuropsychiatric disorders (Raghu, 2021).

## 9. References

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