## Phylogeny

PIP5K1C is a member of the Type I phosphatidylinositol-4-phosphate 5-kinase (PIP5K) family, which also includes the PIP5K1A and PIP5K1B isoforms (bout2009pip5kdrivenptdins(45)p2synthesis pages 1-2, brown2011phylogenomicsofphosphoinositide pages 3-4, xia2011thelocalisationand pages 31-36). This family is part of the larger phosphoinositide kinase (PIK) superfamily (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11). Phylogenetically, PIP kinases form a distinct family within the PIKs, separate from the PI3K and PI4K families (brown2011phylogenomicsofphosphoinositide pages 1-3, brown2011phylogenomicsofphosphoinositide pages 3-4). Mammalian Type I and Type II PIPKs are homologous to yeast Mss4p (brown2011phylogenomicsofphosphoinositide pages 3-4). While invertebrates and Deuterostomia/Chordata possess a single copy of PIP5K1, the three human isoforms arose from early vertebrate-specific gene duplications (brown2011phylogenomicsofphosphoinositide pages 4-6). According to the Manning et al. (2002) classification, PIP5K1C is a lipid kinase belonging to the phosphatidylinositol phosphate kinase family, which is placed within the ‘other’ group of kinases (bout2009pip5kdrivenptdins(45)p2synthesis pages 1-2, bout2009pip5kdrivenptdins(45)p2synthesis pages 13-13). One source classifies PIP kinases within the AGC group (xia2011thelocalisationand pages 31-36).

## Reaction Catalyzed

PIP5K1C catalyzes the transfer of the γ-phosphate group from ATP to the D-5 position of the inositol ring of its lipid substrate (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11, bout2009pip5kdrivenptdins(45)p2synthesis pages 13-13).

The reaction is: ATP + phosphatidylinositol-4-phosphate (PtdIns4P) → ADP + phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80).

## Cofactor Requirements

The catalytic activity of PIP5K1C requires divalent metal ions as cofactors (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11, shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 1-1). The enzyme typically utilizes Mg²⁺ or Mn²⁺ (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 46-52, xia2011thelocalisationand pages 24-28). Mg²⁺ is considered the primary cofactor for its kinase activity (brown2011phylogenomicsofphosphoinositide pages 7-8). The kinase domain contains a conserved aspartate residue (Asp398) that functions as the Mg²⁺/Mn²⁺ binding site (xia2011thelocalisationand pages 40-46).

## Substrate Specificity

PIP5K1C is a lipid kinase whose primary substrate is phosphatidylinositol 4-phosphate (PtdIns4P) (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11). The enzyme’s activation loop subdomain is a key determinant of substrate specificity, distinguishing its preference for PtdIns(4)P over PtdIns(5)P, the substrate for the related PIP4K family (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). Catalytic efficiency is also influenced by acyl chain selectivity for both the substrate and lipid activators (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 1-1). While PtdIns(4)P is its primary substrate, PIP5K may also utilize other phosphoinositides such as PtdIns(3,4)P2 or PtdIns(3)P (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-2). Information on consensus amino acid substrate motifs is not available in the provided sources.

## Structure

PIP5K1C has a domain organization characterized by a conserved central kinase domain of approximately 340 amino acids, which is flanked by poorly conserved, disordered N- and C-terminal regions (unknownauthors2018theroleof pages 25-29, unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The kinase domains of Type I PIP5K isoforms share approximately 80-82% sequence identity (xia2011thelocalisationand pages 31-36, unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The N-terminus contains a binding site for Rac GTPase, while the C-terminus is subject to alternative splicing and mediates interactions with proteins such as talin (xia2011thelocalisationand pages 31-36).

No crystal structure for human PIP5K1C is described, but the structure of zebrafish PIP5K1α (PDB ID: 4TZ7) is considered representative due to high homology (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The kinase domain contains key conserved sites, including an ATP-binding site at Lys188, a catalytic site at Asp316, and a Mg²⁺/Mn²⁺ binding site at Asp398 (xia2011thelocalisationand pages 40-46). The activation loop is unstructured in the absence of phospholipids and is believed to undergo a conformational change upon lipid binding (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The C-terminal tail of certain splice variants can act as an autoinhibitory domain (xia2011thelocalisationand pages 40-46).

## Regulation

PIP5K1C activity is regulated by post-translational modifications, protein-protein interactions, and allostery.

**Phosphorylation**: Phosphorylation is a key regulatory mechanism with context-dependent effects. - **Activating modifications**: Dephosphorylation by protein phosphatase 1 (PP1) or upon recruitment to the AP-2 complex activates the kinase (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11, xia2011thelocalisationand pages 31-36). Phosphorylation by focal adhesion kinase (FAK) or tyrosine phosphorylation mediated by WASP-Arp2/3 enhances kinase activity (xia2011thelocalisationand pages 40-46). - **Inhibiting modifications**: Autophosphorylation serves as a negative feedback mechanism, decreasing lipid kinase activity by tenfold (xia2011thelocalisationand pages 40-46). Phosphorylation by PKA also inhibits PIP5K activity (xia2011thelocalisationand pages 31-36). - **Site-specific regulation**: Phosphorylation at residues Y649 and S650 by kinases including Src and Cdk5 regulates the interaction with talin (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7).

**Other Modifications**: The stability of PIP5K1C is modulated by ubiquitin ligases such as NEDD4 (jin2023lipidkinasespip5ks pages 5-6). It can also undergo caspase-dependent cleavage (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11).

**Allosteric and Protein Interaction-Based Regulation**: - The C-terminal tail of the Iγ\_i2 splice variant functions as an autoinhibitory domain that is relieved upon binding to talin (xia2011thelocalisationand pages 40-46). - Small GTPases of the Rho (RhoA, Rac1, Cdc42) and ARF families directly interact with and modulate PIP5K1C activity and localization (xia2011thelocalisationand pages 31-36). Rac1 binding enhances PtdIns(4,5)P2 synthesis (xia2011thelocalisationand pages 31-36). - Interaction with the retinoblastoma protein (pRB) enhances its kinase activity (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7).

## Function

PIP5K1C is highly expressed in the brain (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). Its expression is altered in multiple cancers, including breast cancer (jin2023lipidkinasespip5ks pages 5-6).

The enzyme catalyzes the synthesis of PtdIns(4,5)P2, a critical lipid second messenger that regulates numerous cellular processes and signaling pathways (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11). PtdIns(4,5)P2 is a substrate for the PI3K/Akt and PLC pathways and is involved in the activation of the NF-kB and p38 MAPK pathways (jin2023lipidkinasespip5ks pages 5-6, jin2023lipidkinasespip5ks pages 6-7, bout2009pip5kdrivenptdins(45)p2synthesis pages 7-8).

PIP5K1C interacts with a variety of proteins, including the focal adhesion protein talin, the tumor suppressor pRB, small GTPases (Rac, Rho, ARF families), EGFR, Src kinase, and clathrin-adaptor complexes (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7, jin2023lipidkinasespip5ks pages 5-6, xia2011thelocalisationand pages 40-46, xia2011thelocalisationand pages 31-36).

Its functional roles include the regulation of cytoskeletal organization, membrane trafficking (clathrin-mediated endocytosis, phagocytosis, synaptic vesicle recycling), cell adhesion, neurite outgrowth, and cell cycle progression (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11, bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). In cancer cells, it promotes migration, invasion, and proliferation (jin2023lipidkinasespip5ks pages 5-6).

## Inhibitors

The small-molecule inhibitor UNC3230 has been identified for PIP5K1C (jin2023lipidkinasespip5ks pages 6-7). It acts as a competitive inhibitor of ATP binding but exhibits dual activity, showing higher potency for the related kinase PIP4Kγ. UNC3230 is limited by a narrow efficacy window and low solubility (jin2023lipidkinasespip5ks pages 6-7).

## Other Comments

Alterations in PIP5K1C activity and PtdIns(4,5)P2 metabolism are associated with cancer and neurological diseases (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). The kinase is implicated in breast cancer progression, particularly in triple-negative breast cancer where it transcriptionally upregulates the immune checkpoint gene PD-L1 (jin2023lipidkinasespip5ks pages 5-6).

A human missense mutation (G757A) in the kinase domain of PIP5K1C causes lethal congenital contractural syndrome type 3 (LCCS3), which is characterized by severe neurodevelopmental defects (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). Knockout mouse models of PIP5K1C display phenotypes ranging from perinatal death to embryonic lethality, underscoring its critical role in brain function and development (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7).

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