1. Phylogeny  
   Phosphatidylinositol 4‐phosphate 5‐kinase type‐1 alpha (PIP5K1A) is a member of the type I phosphatidylinositol phosphate kinase family, a group of enzymes that is evolutionarily conserved across eukaryotes. Orthologs of PIP5K1A have been identified in species ranging from lower eukaryotes such as yeast to higher vertebrates including zebrafish and mammals, with comparisons showing that its core kinase domain exhibits roughly 80% sequence conservation among the type I isoforms. This evolutionary conservation underscores the requirement for preserving the catalytic machinery essential for phosphorylation of phosphatidylinositol 4‐phosphate (PI4P) in order to generate phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2) as part of a primordial signaling network. In phylogenomic analyses, the type I PIP kinases are positioned in a clade distinct from type II PIP4 kinases and other related lipid kinase families such as the class I phosphoinositide 3‐kinases (PI3Ks), reflecting differences in substrate specificity and subcellular localization. Comparative studies indicate that the domain organization, particularly the conserved kinase and dimerization domains, has been retained from the Last Eukaryotic Common Ancestor (LECA) to modern vertebrates, positioning PIP5K1A as an integral component of the ancient phosphoinositide signaling machinery (burke2023beyondpi3kstargeting pages 7-8, nakadatsukui2019phosphatidylinositolkinasesand pages 12-13, brown2011phylogenomicsofphosphoinositide pages 1-3, schramp2012pipkinasesfrom pages 1-4).
2. Reaction Catalyzed  
   PIP5K1A catalyzes the phosphorylation of phosphatidylinositol 4‐phosphate (PI4P) by transferring a phosphate group from ATP to the D5 hydroxyl position of the inositol ring, thereby producing phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2) and ADP. In chemical terms, the reaction can be summarized as:  
     ATP + PI4P → ADP + PI(4,5)P2  
   This reaction is of central importance, as PI(4,5)P2 functions both as a key signaling molecule in its own right and as a precursor for the production of secondary messengers including inositol 1,4,5‐trisphosphate (IP3), diacylglycerol (DAG), and phosphatidylinositol 3,4,5‐trisphosphate (PIP3) (burke2023beyondpi3kstargeting pages 1-2, alexander2015theconciseguide pages 61-64).
3. Cofactor Requirements  
   The kinase activity of PIP5K1A is strictly ATP-dependent, with ATP serving as the phosphate donor in the phosphorylation reaction. In addition, efficient catalysis requires the presence of divalent metal ions, typically Mg²⁺, which assist in stabilizing ATP binding and orienting the substrate for proper phosphoryl transfer. These cofactor requirements are common to many members of the kinase superfamily and are critical to the enzyme’s catalytic mechanism (burke2023beyondpi3kstargeting pages 1-2, alexander2015theconciseguide pages 61-64).
4. Substrate Specificity  
   PIP5K1A displays high substrate specificity for phosphatidylinositol 4‐phosphate (PI4P). The enzyme selectively phosphorylates the 5‐hydroxyl group on the inositol ring of PI4P, resulting in the production of PI(4,5)P2. Although in vitro evidence suggests that PIP5K1A is capable of using phosphatidylinositol (PtdIns) as a substrate under certain experimental conditions, PI4P remains its principal substrate in vivo. The specificity is conferred by a combination of conserved structural features—including a dedicated activation loop and a PIP binding domain—that guarantee the precise recognition and phosphorylation of PI4P (burke2023beyondpi3kstargeting pages 7-8, hu2015resolutionofstructure pages 2-3).
5. Structure  
   The three‐dimensional structure of PIP5K1A is organized around a central kinase domain that is partitioned into two lobes: an N‐lobe responsible primarily for ATP binding and a C‐lobe that accommodates the binding of the phospholipid substrate. This kinase domain adopts a protein kinase–like fold with adaptations unique to lipid kinases, including extended loops and membrane‐targeting motifs that enable the enzyme to interact with lipid bilayers. A prominent feature within the kinase domain is the activation loop, which plays an essential role in substrate recognition and regulates both the catalytic activity and the recruitment of PIP5K1A to phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2)–rich membranes. Structural studies, notably those performed on the zebrafish homolog of PIP5K1A, reveal that the activation loop undergoes a conformational change upon membrane association, adopting an amphipathic helical structure that is critical for its function (burke2023beyondpi3kstargeting pages 13-14, hu2015resolutionofstructure pages 2-3).  
   In addition to the kinase core, PIP5K1A contains a dimerization domain, which facilitates the formation of transient dimers. This monomer–dimer equilibrium is modulated by membrane binding; association with PI(4,5)P2–containing membranes favors dimerization, thereby enhancing catalytic efficiency. The enzyme also has intrinsically disordered N‐ and C‐terminal regions that are less conserved and are thought to mediate isoform‐specific subcellular localization and interactions with other regulatory proteins (burke2023beyondpi3kstargeting pages 7-8, schramp2012pipkinasesfrom pages 1-4, nakadatsukui2019phosphatidylinositolkinasesand pages 12-13).  
   Key catalytic residues within the kinase domain include a lysine within the “IIK” motif and conserved aspartate residues that are essential for ATP binding and phosphoryl transfer. These amino acids align with those found in the homologous domains of other protein kinases and are critical for the conserved mechanism of action observed within the PIP kinase family (hu2015resolutionofstructure pages 2-3, schramp2012pipkinasesfrom pages 1-4). Together, these structural elements define the molecular architecture of PIP5K1A and support its precise role in the production of PI(4,5)P2.
6. Regulation  
   The activity of PIP5K1A is controlled by a variety of regulatory mechanisms that ensure the precise spatial and temporal production of PI(4,5)P2. One major regulatory mechanism is dimerization, which is induced by the binding of the enzyme to PI(4,5)P2–enriched membranes. This dimerization event, mediated by the dimerization domain, enhances the catalytic efficiency of PIP5K1A and serves as a switch for its activation (burke2023beyondpi3kstargeting pages 13-14).  
   Post‐translational modifications further refine the regulation of PIP5K1A. Phosphorylation events, for example, modify the conformation of the activation loop and can influence both the enzyme’s activity and its subcellular localization. Although the precise phosphorylation sites and the full spectrum of kinases responsible for these modifications have yet to be completely delineated, available evidence indicates that modifications within the regulatory regions can either stimulate or dampen enzyme activity (burke2023beyondpi3kstargeting pages 27-28, alexander2015theconciseguide pages 61-64).  
   Moreover, PIP5K1A is regulated by its interactions with other proteins that participate in signaling pathways. In T lymphocytes, for instance, PIP5K1A is recruited by the CD28 receptor at the immunological synapse where it contributes to the localized synthesis of PI(4,5)P2, thereby participating directly in the regulation of NF‐κB transcriptional activity and pro‐inflammatory gene expression (burke2023beyondpi3kstargeting pages 13-14). In addition, oncogenic factors such as KRAS and mutant p53 have been reported to interact with PIP5K1A, linking its activity to cancer‐related signaling pathways (burke2023beyondpi3kstargeting pages 13-14, jin2023lipidkinasespip5ks pages 9-9).  
   Experimental efforts to inhibit PIP5K1A using small molecule inhibitors such as ISA‐2011B have provided further insight into its regulation. ISA‐2011B is known to bind with high affinity to PIP5K1A; however, its concurrent inhibition of class I PI3K p110α complicates the interpretation of its effects exclusively on PIP5K1A activity (burke2023beyondpi3kstargeting pages 13-14, jin2023lipidkinasespip5ks pages 6-7). Collectively, these regulatory mechanisms—including membrane‐induced dimerization, post‐translational modifications, and specific protein–protein interactions—ensure that PIP5K1A activity is tightly adjusted in response to cellular signals.
7. Function  
   PIP5K1A is essential for the synthesis of PI(4,5)P2, a pivotal lipid second messenger that underpins a multitude of cellular processes. The PI(4,5)P2 generated by PIP5K1A serves dual roles: it functions directly as a signaling molecule and acts as a precursor for the synthesis of other second messengers such as inositol 1,4,5‐trisphosphate (IP3), diacylglycerol (DAG), and phosphatidylinositol 3,4,5‐trisphosphate (PIP3). In its role as a precursor, PI(4,5)P2 is utilized by phospholipase C (PLC) to generate IP3 and DAG, which are critical for calcium signaling and protein kinase C activation, while its conversion to PIP3 by PI3K triggers downstream pathways involved in cell growth and survival (burke2023beyondpi3kstargeting pages 1-2, alexander2015theconciseguide pages 61-64).  
   At the plasma membrane, PI(4,5)P2 is a key regulator of actin cytoskeleton dynamics, vesicle trafficking, and cell adhesion. PIP5K1A is particularly important in these contexts, as the locally synthesized PI(4,5)P2 interacts with actin‐binding proteins and regulators of endocytosis and exocytosis, thereby ensuring proper membrane dynamics and the maintenance of cell shape and motility (burke2023beyondpi3kstargeting pages 7-8, jin2023lipidkinasespip5ks pages 9-9).  
   In immune cells, particularly T lymphocytes, PIP5K1A is recruited to the immunological synapse via interactions with receptor complexes such as CD28. Here, it regulates the synthesis of PI(4,5)P2, which in turn modulates intracellular signaling pathways that culminate in the activation of NF‐κB and the transcription of pro‐inflammatory genes, thereby contributing to immune cell activation (burke2023beyondpi3kstargeting pages 13-14).  
   Furthermore, in oncogenic contexts, aberrant expression or activity of PIP5K1A has been associated with cancer progression. Elevated levels of PIP5K1A have been correlated with poor patient outcomes in both prostate and breast cancers. This association is attributed to the enzyme’s role in sustaining oncogenic signaling pathways, including the PI3K/AKT cascade, which is fueled by the availability of PI(4,5)P2 (burke2023beyondpi3kstargeting pages 13-14, jin2023lipidkinasespip5ks pages 9-9, tariq2021strikingabalance pages 3-4).  
   In addition to its cytoplasmic roles, PIP5K1A also has functions in the nucleus where the locally generated PI(4,5)P2 influences chromatin organization and transcription. Interactions with nuclear proteins such as p53 and the polyadenylation factor Star‐PAP further integrate PIP5K1A into signaling networks that regulate gene expression and cellular stress responses (hu2015resolutionofstructure pages 2-3).  
   Thus, the functional repertoire of PIP5K1A encompasses the regulation of fundamental cellular processes including signal transduction, cytoskeletal rearrangement, vesicle trafficking, immune responses, and the maintenance of normal cell growth, highlighting its central role in cellular homeostasis (burke2023beyondpi3kstargeting pages 26-27, jin2023lipidkinasespip5ks pages 9-9).
8. Other Comments  
   Experimental inhibitors such as ISA‐2011B have been employed to target PIP5K1A activity in preclinical studies; however, the lack of absolute specificity of these compounds—owing to off‐target inhibition of related kinases like class I PI3K p110α—remains a challenge for the interpretation of functional studies (burke2023beyondpi3kstargeting pages 13-14, jin2023lipidkinasespip5ks pages 6-7). Research is ongoing to develop more selective inhibitors that can effectively modulate PIP5K1A activity without unintended interference with parallel signaling pathways.  
   Dysregulation of PIP5K1A has been implicated in various disease contexts, most notably in certain cancers such as prostate and breast cancer, where overexpression of the enzyme is associated with enhanced tumor cell proliferation, migration, and resistance to apoptosis. Although specific disease‐associated mutations in the PIP5K1A gene have not been comprehensively described in the available literature, alterations in its expression and activity are recognized as contributing factors to oncogenic signaling cascades.  
   Moreover, studies investigating the molecular signatures of the PIP kinase family have identified distinct sequence motifs that differentiate the isoforms, providing insights into the evolutionary divergence and specialized functions of PIP5K1A relative to its paralogs. Interaction networks between PIP5K1A and other phosphoinositide kinases, particularly the inhibitory interactions with PIP4K family members, further illustrate the complex regulatory circuits that maintain phosphoinositide homeostasis within the cell (khadka2019novelmolecularsignatures pages 20-21, wang2019pip4kssuppressinsulin pages 10-14, lentini2025inositolandpip2pip3 pages 9-10).
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