1. Phylogeny  
   PIP5K1C, encoded by the KIAA0589 gene and commonly referred to as Type I phosphatidylinositol 4‐phosphate 5‐kinase gamma, is a member of the type I phosphatidylinositol phosphate kinase family that catalyzes the formation of phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2) from phosphatidylinositol 4‐phosphate (PI4P) (brown2011phylogenomicsofphosphoinositide pages 4-6). Phylogenomic analyses indicate that type I PIP kinases are evolutionarily conserved across eukaryotic taxa, with orthologous proteins identified in organisms as divergent as yeast (where the homolog is known as MSS4), invertebrates such as Caenorhabditis elegans and Drosophila melanogaster, and all vertebrates including mammals (brown2011phylogenomicsofphosphoinositide pages 12-13). The expansion within vertebrates into three distinct isoforms—PIP5K1A, PIP5K1B, and PIP5K1C—reflects early gene duplication events that contributed to the specialization of phosphoinositide signaling mechanisms (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). Furthermore, the conservation of the central kinase catalytic domain and the regulatory activation loop across the isoforms underscores a shared evolutionary origin that distinguishes type I PIP kinases from other members of the lipid kinase superfamily, such as type II PIP4Ks and PI3Ks (brown2011phylogenomicsofphosphoinositide pages 3-4).
2. Reaction Catalyzed  
   PIP5K1C catalyzes the phosphorylation reaction in which ATP donates a phosphate group to the 5-hydroxyl position of the inositol ring in PI4P, thereby converting PI4P to PI(4,5)P2 and yielding ADP as a product (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11). This chemical reaction plays a central role in the generation of PI(4,5)P2, a pivotal lipid second messenger in cellular signaling (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-2).
3. Cofactor Requirements  
   The enzymatic activity of PIP5K1C is strictly ATP-dependent, with ATP serving as the phosphate donor in the phosphorylation reaction (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 1-2). In addition to ATP, the presence of magnesium ions (Mg²⁺) is required as an essential cofactor to stabilize ATP binding and facilitate the transfer of the phosphate group (wright2015developmentofa pages 2-3).
4. Substrate Specificity  
   PIP5K1C displays high substrate specificity by phosphorylating PI4P at its D-5 position on the inositol ring to generate PI(4,5)P2 (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). The kinase exhibits acyl chain selectivity; kinetic studies have demonstrated that PIP5K1C preferentially utilizes PI4P species containing unsaturated fatty acyl chains—for instance, substrates with a 1-stearoyl-2-arachidonoyl configuration exhibit significantly lower Km values and enhanced catalytic efficiency compared to fully saturated phosphoinositide forms (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 2-3). Moreover, the enzyme’s activity is modulated by the lipid environment, such that the presence of specific phosphatidic acid species with defined acyl chain compositions can allosterically activate PIP5K1C; this interplay between substrate acyl chain composition and activator lipid characteristics is critical for generating physiologically relevant PI(4,5)P2 pools in cellular membranes (bout2009pip5kdrivenptdins(45)p2synthesis pages 7-8, shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 8-9).
5. Structure  
   PIP5K1C is characterized by a well-defined central kinase domain that houses the catalytic machinery responsible for the transfer of a phosphate group from ATP to PI4P (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). Structural studies of related isoforms, such as PIP5K1A, have revealed that the kinase domain adopts a bilobed architecture consisting of an N-terminal lobe principally involved in ATP binding and a larger C-terminal lobe that contributes to substrate binding and catalytic activity (hu2015resolutionofstructure pages 2-3). Within this domain, several conserved motifs—such as the phosphate-binding loop (P-loop), the catalytic loop, and most notably the activation loop—are critical for enzymatic function; the activation loop in PIP5K1C is proposed to dictate substrate specificity and plays a role in membrane recruitment by undergoing a conformational transition upon phospholipid interaction (doughman2003phosphatidylinositolphosphatekinases pages 1-3). In addition, a unique polybasic region in the C-terminal segment of the protein mediates association with the plasma membrane and facilitates interactions with regulatory proteins, including talin, which is important for targeting the kinase to focal adhesions (bout2009pip5kdrivenptdins(45)p2synthesis pages 9-10). Structural analyses further suggest that PIP5K isoforms are capable of forming homodimers, and such dimerization has been implicated in the allosteric regulation of kinase activity by stabilizing an active conformation of the catalytic domain (hu2015resolutionofstructure pages 8-9).
6. Regulation  
   Regulatory mechanisms governing PIP5K1C activity are multifactorial and include post-translational modifications, interactions with regulatory proteins, and lipid-mediated allosteric effects. Phosphorylation plays a central role in modulating PIP5K1C function; for example, phosphorylation at specific residues—such as tyrosine 649 and serine 650 in some splice variants—has been shown to regulate binding affinity for talin, thereby influencing focal adhesion dynamics and subsequent actin remodeling (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). In addition to phosphorylation by kinases such as Src and cyclin-dependent kinase 5 (Cdk5), PIP5K1C is capable of autophosphorylation, a modification that has been documented to reduce its kinase activity (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7). Protein-protein interactions also play a significant regulatory role; the polybasic C-terminal region of PIP5K1C mediates binding to small GTPases such as Rac, which, independent of its nucleotide-bound state, modulates the spatial localization and catalytic efficiency of the enzyme at the plasma membrane (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). Furthermore, allosteric activation by lipid molecules—most notably phosphatidic acid—has been demonstrated to enhance PIP5K1C activity in a manner that is dependent on the acyl chain composition of both the substrate lipid and the activator, providing an additional layer of regulation that fine-tunes PI(4,5)P2 synthesis in response to dynamic changes in the membrane environment (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 6-8).
7. Function  
   The biological function of PIP5K1C centers on its role in generating PI(4,5)P2, a critical lipid second messenger that regulates a multitude of cellular processes. By catalyzing the phosphorylation of PI4P, PIP5K1C ensures the local production of PI(4,5)P2, which in turn plays key roles in signal transduction pathways, vesicle trafficking, and the dynamic reorganization of the actin cytoskeleton (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4). The spatial and temporal regulation of PI(4,5)P2 synthesis by PIP5K1C is essential for sustaining receptor-mediated signaling events; for instance, the localized accumulation of PI(4,5)P2 at the plasma membrane is required for phagocytosis, where distinct pools of the lipid regulate sequential steps in actin remodeling and receptor clustering (bout2009pip5kdrivenptdins(45)p2synthesis pages 9-10). In addition, PIP5K1C is implicated in the modulation of cell adhesion by contributing to focal adhesion assembly via its interaction with talin, thereby influencing cell motility and the spatial organization of the cytoskeleton (bura2023aplethoraof pages 8-9). Neuronal functions are also influenced by PIP5K1C; studies have linked its high expression in brain tissue to the regulation of synaptic vesicle recycling and neurite outgrowth, processes that are dependent on tightly controlled PI(4,5)P2 dynamics (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7, jin2023lipidkinasespip5ks pages 9-9). Together, these functions underscore the central role of PIP5K1C in orchestrating cellular responses that require rapid and localized changes in membrane lipid composition.
8. Other Comments  
   Owing to its pivotal role in PI(4,5)P2 synthesis, PIP5K1C has attracted considerable attention as a potential therapeutic target. Mutations in PIP5K1C have been linked to congenital contractural syndrome type 3 (LCCS3), a severe developmental disorder characterized by multiple joint contractures, muscle wasting, and motor neuron pathology (chen2022theroleof pages 11-12). In addition, the enzyme’s involvement in regulating actin dynamics and focal adhesion formation has spurred interest in targeting PIP5K1C in pathological conditions such as cancer and pain syndromes, where aberrant actin remodeling and cell adhesion contribute to disease progression (burke2023beyondpi3kstargeting pages 26-27). Although most inhibitor development efforts have focused on the closely related PIP5K1A isoform, recent advances in assay development using high-throughput screening approaches have provided a framework for the identification of selective inhibitors that could potentially be applied to PIP5K1C (stratker2020developmentofan pages 7-10). These inhibitors promise to further elucidate the kinase’s role in cellular signaling and may also serve as the basis for future drug discovery initiatives targeting disorders attributed to dysregulated phosphoinositide metabolism.
9. References
10. I. van den Bout and N. Divecha, “Pip5k-driven ptdins(4,5)P2 synthesis: regulation and cellular functions,” Journal of Cell Science, vol. 122, pp. 3837–3850, Nov. 2009, doi:10.1242/jcs.056127.
11. J. R. Brown and K. R. Auger, “Phylogenomics of phosphoinositide lipid kinases: perspectives on the evolution of second messenger signaling and drug discovery,” BMC Evolutionary Biology, vol. 11, pp. 4–4, Jan. 2011, doi:10.1186/1471-2148-11-4.
12. A. Bura, S. Čabrijan, I. Đurić, T. Bruketa, and A. Jurak Begonja, “A plethora of functions condensed into tiny phospholipids: the story of pi4p and pi(4,5)p2,” Cells, vol. 12, p. 1411, May 2023, doi:10.3390/cells12101411.
13. J. E. Burke, J. Triscott, B. M. Emerling, and G. R. V. Hammond, “Beyond pi3ks: targeting phosphoinositide kinases in disease,” Nature Reviews Drug Discovery, vol. 22, pp. 357–386, Nov. 2023, doi:10.1038/s41573-022-00582-5.
14. Y. V. Shulga, R. Anderson, M. Topham, and R. Epand, “Phosphatidylinositol-4-phosphate 5-kinase isoforms exhibit acyl chain selectivity for both substrate and lipid activator\*,” The Journal of Biological Chemistry, vol. 287, pp. 35953–35963, Sep. 2012, doi:10.1074/jbc.m112.370155.
15. J. Hu, Q. Yuan, X. Kang, Y. Qin, L. Li, Y. Ha, and D. Wu, “Resolution of structure of pip5k1a reveals molecular mechanism for its regulation by dimerization and dishevelled,” Nature Communications, Sep. 2015, doi:10.1038/ncomms9205.
16. Y. Jin and J. Xue, “Lipid kinases pip5ks and pip4ks: potential drug targets for breast cancer,” Frontiers in Oncology, Dec. 2023, doi:10.3389/fonc.2023.1323897.
17. A. Liu, D. Sui, D. Wu, and J. Hu, “The activation loop of pip5k functions as a membrane sensor essential for lipid substrate processing,” Science Advances, Nov. 2016, doi:10.1126/sciadv.1600925.
18. R. L. Doughman, A. J. Firestone, and R. Anderson, “Phosphatidylinositol phosphate kinases put pi4,5p2 in its place,” The Journal of Membrane Biology, vol. 194, pp. 77–89, Jul. 2003, doi:10.1007/s00232-003-2027-7.
19. K. Strätker, S. Haidar, Á. Amesty, E. El‐Awaad, C. Götz, A. Estévez‐Braun, and J. Jose, “Development of an in vitro screening assay for pip5k1α lipid kinase and identification of potent inhibitors,” The FEBS Journal, vol. 287, pp. 3042–3064, Jan. 2020, doi:10.1111/febs.15194.
20. C. Chen, J. Hu, and K. Ling, “The role of primary cilia-associated phosphoinositide signaling in development,” Journal of Developmental Biology, Dec. 2022, doi:10.3390/jdb10040051.

References

1. (bout2009pip5kdrivenptdins(45)p2synthesis pages 10-11): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
2. (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
3. (bout2009pip5kdrivenptdins(45)p2synthesis pages 6-7): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
4. (brown2011phylogenomicsofphosphoinositide pages 4-6): James R Brown and Kurt R Auger. Phylogenomics of phosphoinositide lipid kinases: perspectives on the evolution of second messenger signaling and drug discovery. BMC Evolutionary Biology, 11:4-4, Jan 2011. URL: https://doi.org/10.1186/1471-2148-11-4, doi:10.1186/1471-2148-11-4. This article has 129 citations.
5. (bura2023aplethoraof pages 8-9): Anica Bura, Sara Čabrijan, Iris Đurić, Tea Bruketa, and Antonija Jurak Begonja. A plethora of functions condensed into tiny phospholipids: the story of pi4p and pi(4,5)p2. Cells, 12:1411, May 2023. URL: https://doi.org/10.3390/cells12101411, doi:10.3390/cells12101411. This article has 9 citations and is from a peer-reviewed journal.
6. (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 1-2): Yulia V. Shulga, R. Anderson, M. Topham, and R. Epand. Phosphatidylinositol-4-phosphate 5-kinase isoforms exhibit acyl chain selectivity for both substrate and lipid activator\*. The Journal of Biological Chemistry, 287:35953-35963, Sep 2012. URL: https://doi.org/10.1074/jbc.m112.370155, doi:10.1074/jbc.m112.370155. This article has 68 citations.
7. (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 2-3): Yulia V. Shulga, R. Anderson, M. Topham, and R. Epand. Phosphatidylinositol-4-phosphate 5-kinase isoforms exhibit acyl chain selectivity for both substrate and lipid activator\*. The Journal of Biological Chemistry, 287:35953-35963, Sep 2012. URL: https://doi.org/10.1074/jbc.m112.370155, doi:10.1074/jbc.m112.370155. This article has 68 citations.
8. (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 6-8): Yulia V. Shulga, R. Anderson, M. Topham, and R. Epand. Phosphatidylinositol-4-phosphate 5-kinase isoforms exhibit acyl chain selectivity for both substrate and lipid activator\*. The Journal of Biological Chemistry, 287:35953-35963, Sep 2012. URL: https://doi.org/10.1074/jbc.m112.370155, doi:10.1074/jbc.m112.370155. This article has 68 citations.
9. (wright2015developmentofa pages 2-3): Brittany D. Wright, Catherine Simpson, Michael Stashko, Dmitri Kireev, Emily A. Hull-Ryde, Mark J. Zylka, and William P. Janzen. Development of a high-throughput screening assay to identify inhibitors of the lipid kinase pip5k1c. SLAS Discovery, 20:655-662, Jun 2015. URL: https://doi.org/10.1177/1087057114564057, doi:10.1177/1087057114564057. This article has 24 citations and is from a peer-reviewed journal.
10. (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-2): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
11. (bout2009pip5kdrivenptdins(45)p2synthesis pages 7-8): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
12. (bout2009pip5kdrivenptdins(45)p2synthesis pages 9-10): Iman van den Bout and Nullin Divecha. Pip5k-driven ptdins(4,5)p2 synthesis: regulation and cellular functions. Journal of Cell Science, 122:3837-3850, Nov 2009. URL: https://doi.org/10.1242/jcs.056127, doi:10.1242/jcs.056127. This article has 380 citations and is from a domain leading peer-reviewed journal.
13. (brown2011phylogenomicsofphosphoinositide pages 12-13): James R Brown and Kurt R Auger. Phylogenomics of phosphoinositide lipid kinases: perspectives on the evolution of second messenger signaling and drug discovery. BMC Evolutionary Biology, 11:4-4, Jan 2011. URL: https://doi.org/10.1186/1471-2148-11-4, doi:10.1186/1471-2148-11-4. This article has 129 citations.
14. (brown2011phylogenomicsofphosphoinositide pages 3-4): James R Brown and Kurt R Auger. Phylogenomics of phosphoinositide lipid kinases: perspectives on the evolution of second messenger signaling and drug discovery. BMC Evolutionary Biology, 11:4-4, Jan 2011. URL: https://doi.org/10.1186/1471-2148-11-4, doi:10.1186/1471-2148-11-4. This article has 129 citations.
15. (burke2023beyondpi3kstargeting pages 26-27): John E. Burke, Joanna Triscott, Brooke M. Emerling, and Gerald R. V. Hammond. Beyond pi3ks: targeting phosphoinositide kinases in disease. Nature Reviews Drug Discovery, 22:357-386, Nov 2023. URL: https://doi.org/10.1038/s41573-022-00582-5, doi:10.1038/s41573-022-00582-5. This article has 89 citations and is from a highest quality peer-reviewed journal.
16. (chen2022theroleof pages 11-12): Chuan Chen, Jinghua Hu, and Kun Ling. The role of primary cilia-associated phosphoinositide signaling in development. Journal of Developmental Biology, Dec 2022. URL: https://doi.org/10.3390/jdb10040051, doi:10.3390/jdb10040051. This article has 5 citations and is from a peer-reviewed journal.
17. (doughman2003phosphatidylinositolphosphatekinases pages 1-3): Renee L. Doughman, Ari J. Firestone, and R. Anderson. Phosphatidylinositol phosphate kinases put pi4,5p2 in its place. The Journal of Membrane Biology, 194:77-89, Jul 2003. URL: https://doi.org/10.1007/s00232-003-2027-7, doi:10.1007/s00232-003-2027-7. This article has 334 citations.
18. (hu2015resolutionofstructure pages 2-3): Jian Hu, Qianying Yuan, Xue Kang, Yuanbo Qin, Lin Li, Y. Ha, and Dianqing Wu. Resolution of structure of pip5k1a reveals molecular mechanism for its regulation by dimerization and dishevelled. Nature Communications, Sep 2015. URL: https://doi.org/10.1038/ncomms9205, doi:10.1038/ncomms9205. This article has 59 citations and is from a highest quality peer-reviewed journal.
19. (hu2015resolutionofstructure pages 8-9): Jian Hu, Qianying Yuan, Xue Kang, Yuanbo Qin, Lin Li, Y. Ha, and Dianqing Wu. Resolution of structure of pip5k1a reveals molecular mechanism for its regulation by dimerization and dishevelled. Nature Communications, Sep 2015. URL: https://doi.org/10.1038/ncomms9205, doi:10.1038/ncomms9205. This article has 59 citations and is from a highest quality peer-reviewed journal.
20. (jin2023lipidkinasespip5ks pages 9-9): Yue Jin and Jian Xue. Lipid kinases pip5ks and pip4ks: potential drug targets for breast cancer. Frontiers in Oncology, Dec 2023. URL: https://doi.org/10.3389/fonc.2023.1323897, doi:10.3389/fonc.2023.1323897. This article has 2 citations and is from a peer-reviewed journal.
21. (shulga2012phosphatidylinositol4phosphate5kinaseisoforms pages 8-9): Yulia V. Shulga, R. Anderson, M. Topham, and R. Epand. Phosphatidylinositol-4-phosphate 5-kinase isoforms exhibit acyl chain selectivity for both substrate and lipid activator\*. The Journal of Biological Chemistry, 287:35953-35963, Sep 2012. URL: https://doi.org/10.1074/jbc.m112.370155, doi:10.1074/jbc.m112.370155. This article has 68 citations.
22. (stratker2020developmentofan pages 7-10): Katja Strätker, Samer Haidar, Ángel Amesty, Ehab El‐Awaad, Claudia Götz, Ana Estévez‐Braun, and Joachim Jose. Development of an in vitro screening assay for pip5k1α lipid kinase and identification of potent inhibitors. The FEBS Journal, 287:3042-3064, Jan 2020. URL: https://doi.org/10.1111/febs.15194, doi:10.1111/febs.15194. This article has 14 citations.