1. Phylogeny  
   Phosphatidylinositol 4‐phosphate 5‐kinase‐like protein 1 (PIP5KL1) is classified within the type I phosphatidylinositol phosphate kinase (PIPK) family. Sequence analyses and phylogenomic studies have demonstrated that type I PIP kinases are evolutionarily conserved across metazoans, with ancestral gene duplication events in early vertebrate evolution giving rise to multiple isoforms, including PIP5K1A, PIP5K1B, and PIP5KL1 (shi2010overexpressionofpip5kl1 pages 1-2, brown2011phylogenomicsofphosphoinositide pages 1-3). Although PIP5KL1 shares homology with other catalytically active members of the family through a conserved central kinase domain, it has diverged such that it no longer exhibits full intrinsic catalytic activity. Instead, it appears to have evolved primarily to function as a regulatory scaffold. This divergence is documented in comparative kinome analyses showing that while most type I kinases retain both catalytic and regulatory functions, PIP5KL1 is set apart by truncations in conserved catalytic motifs, a feature that is consistent with its specialized role in modulating phosphoinositide metabolism rather than directly catalyzing phosphate transfer (shi2010overexpressionofpip5kl1 pages 1-2, brown2011phylogenomicsofphosphoinositide pages 3-4, scheeff2005structuralevolutionof pages 19-20).
2. Reaction Catalyzed  
   The canonical reaction catalyzed by type I phosphatidylinositol phosphate kinases involves the transfer of a phosphate group from adenosine triphosphate (ATP) to phosphatidylinositol 4‐phosphate (PI(4)P), thereby generating phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2) and producing adenosine diphosphate (ADP) along with a proton (H⁺) as a by‐product. Although PIP5KL1 itself exhibits minimal intrinsic catalytic activity, it plays an essential role by serving as a scaffold to recruit and position active type I PIP kinases at distinct cellular compartments where they can perform the following reaction:  
     ATP + PI(4)P → ADP + PI(4,5)P2 + H⁺  
   This reaction is fundamental to the production of PI(4,5)P2, which in turn is a precursor for PI(3,4,5)P3 synthesis and is crucial for orchestrating actin nucleation, membrane dynamics, and downstream signal transduction (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, doughman2003phosphatidylinositolphosphatekinases pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of type I phosphatidylinositol phosphate kinases is generally dependent on divalent cations, with magnesium (Mg²⁺) being the essential cofactor. Mg²⁺ interacts with ATP in the active site, stabilizing the phosphoryl transfer reaction required for PI(4,5)P2 synthesis. Although PIP5KL1 itself does not display significant catalytic activity, it functions in close association with active kinases whose reactions require Mg²⁺ (doughman2003phosphatidylinositolphosphatekinases pages 1-3, hu2015resolutionofstructure pages 1-2, shi2010overexpressionofpip5kl1 pages 6-8).
4. Substrate Specificity  
   Type I phosphatidylinositol phosphate kinases exhibit a substrate specificity that favors the phosphorylation of phosphatidylinositol 4‐phosphate (PI(4)P) at the D5 hydroxyl position, resulting in the formation of phosphatidylinositol 4,5‐bisphosphate (PI(4,5)P2). This specificity is largely dictated by conserved sequences within the enzyme’s activation loop, which contains consensus motifs responsible for recognizing the inositol ring of PI(4)P (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, doughman2003phosphatidylinositolphosphatekinases pages 1-3). Although PIP5KL1 is not catalytically robust on its own, it retains structural features that allow it to associate with catalytically active type I PIP kinases, thereby indirectly ensuring that the correct lipid substrate, PI(4)P, is phosphorylated in a spatially controlled manner. This protein–protein interaction promotes the localized formation of PI(4,5)P2, which is critical for subsequent conversion into PI(3,4,5)P3 and the initiation of downstream signaling cascades (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, doughman2003phosphatidylinositolphosphatekinases pages 1-3, shi2010overexpressionofpip5kl1 pages 9-10).
5. Structure  
   PIP5KL1 contains a central kinase-like domain that is homologous to those found in catalytically active type I phosphatidylinositol phosphate kinases; however, several key catalytic residues are missing, which accounts for its lack of robust kinase activity (shi2010overexpressionofpip5kl1 pages 1-2, doughman2003phosphatidylinositolphosphatekinases pages 1-3). In structurally characterized type I PIP kinases, the enzyme typically exhibits a two-lobe architecture comprising an N-terminal lobe that houses a glycine-rich loop for ATP binding and a C-terminal lobe that contains the activation loop, a conserved lysine essential for catalysis, and additional residues implicated in substrate binding and membrane association. Although no direct high-resolution structure of PIP5KL1 has been reported, homology modeling based on related kinases such as PIP5K1A suggests that PIP5KL1 adopts a similar overall fold with an incomplete catalytic core. This structural arrangement is consistent with its role as a scaffold: the preserved portions of the kinase-like domain facilitate interactions with other type I PIP kinases, enabling proper localization at the plasma membrane and specific intracellular compartments, while the absence of fully conserved catalytic motifs underlies its minimal intrinsic phosphotransfer capability (hu2015resolutionofstructure pages 1-2, shi2010overexpressionofpip5kl1 pages 1-2, scheeff2005structuralevolutionof pages 19-20).
6. Regulation  
   Regulatory mechanisms governing PIP5KL1 function primarily involve its expression levels and its capacity to form complexes with catalytically active type I PIP kinases. In human gastric cancer cells, overexpression studies have demonstrated that elevated levels of PIP5KL1 correlate with a marked suppression of cell proliferation and migration; these effects are accompanied by a decrease in serum-induced AKT1 phosphorylation, indicating modulation of downstream signaling pathways (shi2010overexpressionofpip5kl1 pages 1-2, shi2010overexpressionofpip5kl1 pages 8-9). In hepatic systems, PIP5KL1 participates in protein–protein interactions with low-density lipoprotein receptor-related protein 1 (LRP1), which recruits PIP5K1β to the plasma membrane, thereby ensuring adequate synthesis of PI(4,5)P2. This localization is critical for maintaining phosphoinositide levels that support proper mitochondrial dynamics and lipid homeostasis (chinnarasu2021hepaticldlreceptorrelated pages 6-7, jaeschke2021ldlreceptorrelatedprotein pages 1-3). Overall, regulation of PIP5KL1 involves its ability to modulate the activity and spatial distribution of active kinases without undergoing significant post-translational modifications itself, as current reports do not detail specific phosphorylation or ubiquitination events on PIP5KL1 (shi2010overexpressionofpip5kl1 pages 6-8, jaeschke2021ldlreceptorrelatedprotein pages 3-4, wang2006cellbasedscreeningand pages 2-3).
7. Function  
   PIP5KL1 plays a critical role as a scaffold protein within the phosphoinositide signaling cascade. Its primary function is to localize and regulate active type I PI(4)P 5-kinases at specific plasma membrane microdomains and other intracellular compartments, ensuring the localized generation of phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2). The production of PI(4,5)P2 is essential for numerous cellular processes, including actin nucleation, focal adhesion dynamics, and the generation of PI(3,4,5)P3 via phosphorylation by phosphoinositide 3-kinase (PI3K), thereby linking PIP5KL1 to critical signal transduction pathways (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, doughman2003phosphatidylinositolphosphatekinases pages 1-3). In human gastric cancer cells, overexpression of PIP5KL1 has been shown to suppress cell proliferation and migration, indicating a tumor suppressor role that is mediated through decreased AKT1 signaling (shi2010overexpressionofpip5kl1 pages 1-2, shi2010overexpressionofpip5kl1 pages 8-9). Furthermore, in liver cells, PIP5KL1 is implicated in the regulation of mitochondrial dynamics through its interaction with LRP1, which facilitates the proper synthesis of PI(4,5)P2 necessary for maintaining organelle integrity (chinnarasu2021hepaticldlreceptorrelated pages 6-7, jaeschke2021ldlreceptorrelatedprotein pages 1-3). Expression studies in neural tissues have also identified PIP5KL1 as a brain-specific, kinase-dead isoform that is expressed during early postnatal development, suggesting a role in the regulation of neuronal morphology and adhesion (muzyka2018postnataldevelopmentaldynamics pages 28-29).
8. Other Comments  
   To date, there are no reported small-molecule inhibitors that target PIP5KL1 specifically. The literature emphasizes its role as a regulatory scaffold rather than as a direct enzymatic catalyst, and consequently, research efforts have focused on its interactions with catalytically active type I PIP kinases rather than on its inhibition. In the context of disease, reduced PIP5KL1 expression has been associated with gastric cancer progression, supporting its potential tumor suppressor function. Additionally, in hepatocytes, aberrant function of PIP5KL1—as evidenced by its impaired interaction with LRP1—has been linked to altered mitochondrial dynamics and lipid metabolism, which may have ramifications in hepatic pathophysiology. Although detailed post-translational modification sites and mutational analyses have not been extensively described in the provided sources, the available data consistently indicate that PIP5KL1 serves as a key modulator of lipid kinase localization and activity without directly mediating catalytic function (shi2010overexpressionofpip5kl1 pages 1-2, chinnarasu2021hepaticldlreceptorrelated pages 6-7, wang2006cellbasedscreeningand pages 7-8).
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. (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4)
11. 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. (hu2015resolutionofstructure pages 1-2)
12. L. Shi, M. Zhao, Q. Luo, Y.-M. Ma, J.-L. Zhong, X.-H. Yuan, and C.-Z. Huang, “Overexpression of pip5kl1 suppresses cell proliferation and migration in human gastric cancer cells,” Molecular Biology Reports, vol. 37, pp. 2189–2198, Jun. 2010, doi:10.1007/s11033-009-9701-5. (shi2010overexpressionofpip5kl1 pages 1-2, pages 6-8, pages 8-9, pages 9-10)
13. 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, p. 4, Jan. 2011. (brown2011phylogenomicsofphosphoinositide pages 1-3, pages 3-4, pages 7-8, pages 8-9, pages 11-12)
14. S. Chinnarasu, F. Alogaili, K. Bove, A. Jaeschke, and D. Hui, “Hepatic ldl receptor-related protein-1 deficiency alters mitochondrial dynamics through phosphatidylinositol 4,5-bisphosphate reduction,” The Journal of Biological Chemistry, Jan. 2021, doi:10.1016/j.jbc.2021.100370. (chinnarasu2021hepaticldlreceptorrelated pages 6-7)
15. 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. (doughman2003phosphatidylinositolphosphatekinases pages 1-3, pages 3-4)
16. A. Jaeschke and D. Y. Hui, “Ldl receptor-related protein 1 and its interacting partners in tissue homeostasis,” Current Opinion in Lipidology, vol. 32, pp. 301–307, Jul. 2021, doi:10.1097/mol.0000000000000776. (jaeschke2021ldlreceptorrelatedprotein pages 1-3, pages 3-4)
17. V. V. Muzyka, M. Brooks, and T. C. Badea, “Postnatal developmental dynamics of cell type specification genes in brn3a/pou4f1 retinal ganglion cells,” Neural Development, Jun. 2018, doi:10.1186/s13064-018-0110-0. (muzyka2018postnataldevelopmentaldynamics pages 28-29)
18. K. Nakada-Tsukui, N. Watanabe, T. Maehama, and T. Nozaki, “Phosphatidylinositol kinases and phosphatases in entamoeba histolytica,” Frontiers in Cellular and Infection Microbiology, Jun. 2019, doi:10.3389/fcimb.2019.00150. (nakadatsukui2019phosphatidylinositolkinasesand pages 12-13)
19. E. Scheeff and P. Bourne, “Structural evolution of the protein kinase–like superfamily,” PLoS Computational Biology, Sep. 2005, doi:10.1371/journal.pcbi.0010049. (scheeff2005structuralevolutionof pages 19-20, pages 17-18, pages 2-3)
20. L. Wang, X. Gao, P. Gao, W. Deng, P. Yu, J. Ma, J. Guo, X. Wang, H. Cheng, C. Zhang, C. Yu, X. Ma, B. Lv, Y. Lu, T. Shi, and D. Ma, “Cell-based screening and validation of human novel genes associated with cell viability,” SLAS Discovery, vol. 11, pp. 369–376, Jun. 2006, doi:10.1177/1087057106286654. (wang2006cellbasedscreeningand pages 2-3, pages 6-7, pages 7-8)
21. B. Nyesiga and A. G. Wingren, “Pip5k1a (phosphatidylinositol-4-phosphate 5-kinase type 1 alpha),” Atlas of Genetics and Cytogenetics in Oncology and Haematology, Oct. 2018, doi:10.4267/2042/68758. (nyesiga2018pip5k1a(phosphatidylinositol4phosphate5kinase pages 1-2)

References

1. (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.
2. (hu2015resolutionofstructure pages 1-2): 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.
3. (shi2010overexpressionofpip5kl1 pages 1-2): Lan Shi, Mei Zhao, Qing Luo, Yi-Ming Ma, Jia-Ling Zhong, Xing-Hua Yuan, and Chang-Zhi Huang. Overexpression of pip5kl1 suppresses cell proliferation and migration in human gastric cancer cells. Molecular Biology Reports, 37:2189-2198, Jun 2010. URL: https://doi.org/10.1007/s11033-009-9701-5, doi:10.1007/s11033-009-9701-5. This article has 21 citations and is from a peer-reviewed journal.
4. (shi2010overexpressionofpip5kl1 pages 6-8): Lan Shi, Mei Zhao, Qing Luo, Yi-Ming Ma, Jia-Ling Zhong, Xing-Hua Yuan, and Chang-Zhi Huang. Overexpression of pip5kl1 suppresses cell proliferation and migration in human gastric cancer cells. Molecular Biology Reports, 37:2189-2198, Jun 2010. URL: https://doi.org/10.1007/s11033-009-9701-5, doi:10.1007/s11033-009-9701-5. This article has 21 citations and is from a peer-reviewed journal.
5. (brown2011phylogenomicsofphosphoinositide pages 1-3): 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.
6. (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.
7. (chinnarasu2021hepaticldlreceptorrelated pages 6-7): Sivaprakasam Chinnarasu, Fawzi Alogaili, K. Bove, A. Jaeschke, and D. Hui. Hepatic ldl receptor-related protein-1 deficiency alters mitochondrial dynamics through phosphatidylinositol 4,5-bisphosphate reduction. The Journal of Biological Chemistry, Jan 2021. URL: https://doi.org/10.1016/j.jbc.2021.100370, doi:10.1016/j.jbc.2021.100370. This article has 11 citations.
8. (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.
9. (muzyka2018postnataldevelopmentaldynamics pages 28-29): Vladimir Vladimirovich Muzyka, Matthew Brooks, and Tudor Constantin Badea. Postnatal developmental dynamics of cell type specification genes in brn3a/pou4f1 retinal ganglion cells. Neural Development, Jun 2018. URL: https://doi.org/10.1186/s13064-018-0110-0, doi:10.1186/s13064-018-0110-0. This article has 19 citations and is from a peer-reviewed journal.
10. (nakadatsukui2019phosphatidylinositolkinasesand pages 12-13): Kumiko Nakada-Tsukui, Natsuki Watanabe, Tomohiko Maehama, and Tomoyoshi Nozaki. Phosphatidylinositol kinases and phosphatases in entamoeba histolytica. Frontiers in Cellular and Infection Microbiology, Jun 2019. URL: https://doi.org/10.3389/fcimb.2019.00150, doi:10.3389/fcimb.2019.00150. This article has 47 citations and is from a peer-reviewed journal.
11. (scheeff2005structuralevolutionof pages 19-20): Eric Scheeff and Philip Bourne. Structural evolution of the protein kinase–like superfamily. PLoS Computational Biology, Sep 2005. URL: https://doi.org/10.1371/journal.pcbi.0010049, doi:10.1371/journal.pcbi.0010049. This article has 354 citations and is from a highest quality peer-reviewed journal.
12. (shi2010overexpressionofpip5kl1 pages 8-9): Lan Shi, Mei Zhao, Qing Luo, Yi-Ming Ma, Jia-Ling Zhong, Xing-Hua Yuan, and Chang-Zhi Huang. Overexpression of pip5kl1 suppresses cell proliferation and migration in human gastric cancer cells. Molecular Biology Reports, 37:2189-2198, Jun 2010. URL: https://doi.org/10.1007/s11033-009-9701-5, doi:10.1007/s11033-009-9701-5. This article has 21 citations and is from a peer-reviewed journal.
13. (shi2010overexpressionofpip5kl1 pages 9-10): Lan Shi, Mei Zhao, Qing Luo, Yi-Ming Ma, Jia-Ling Zhong, Xing-Hua Yuan, and Chang-Zhi Huang. Overexpression of pip5kl1 suppresses cell proliferation and migration in human gastric cancer cells. Molecular Biology Reports, 37:2189-2198, Jun 2010. URL: https://doi.org/10.1007/s11033-009-9701-5, doi:10.1007/s11033-009-9701-5. This article has 21 citations and is from a peer-reviewed journal.
14. (wang2006cellbasedscreeningand pages 2-3): Lan Wang, Xia Gao, Peng Gao, Weiwei Deng, Peng Yu, Jinjing Ma, Jinhai Guo, Xinyu Wang, Hualing Cheng, Chenying Zhang, Chuanfei Yu, Xi Ma, Bingfeng Lv, Yang Lu, Taiping Shi, and Dalong Ma. Cell-based screening and validation of human novel genes associated with cell viability. SLAS Discovery, 11:369-376, Jun 2006. URL: https://doi.org/10.1177/1087057106286654, doi:10.1177/1087057106286654. This article has 30 citations and is from a peer-reviewed journal.
15. (jaeschke2021ldlreceptorrelatedprotein pages 1-3): Anja Jaeschke and David Y. Hui. Ldl receptor-related protein 1 and its interacting partners in tissue homeostasis. Current Opinion in Lipidology, 32:301-307, Jul 2021. URL: https://doi.org/10.1097/mol.0000000000000776, doi:10.1097/mol.0000000000000776. This article has 11 citations and is from a peer-reviewed journal.
16. (jaeschke2021ldlreceptorrelatedprotein pages 3-4): Anja Jaeschke and David Y. Hui. Ldl receptor-related protein 1 and its interacting partners in tissue homeostasis. Current Opinion in Lipidology, 32:301-307, Jul 2021. URL: https://doi.org/10.1097/mol.0000000000000776, doi:10.1097/mol.0000000000000776. This article has 11 citations and is from a peer-reviewed journal.
17. (nyesiga2018pip5k1a(phosphatidylinositol4phosphate5kinase pages 1-2): Barnabas Nyesiga and Anette Görloff Wingren. Pip5k1a (phosphatidylinositol-4-phosphate 5-kinase type 1 alpha). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Oct 2018. URL: https://doi.org/10.4267/2042/68758, doi:10.4267/2042/68758. This article has 0 citations and is from a peer-reviewed journal.
18. (wang2006cellbasedscreeningand pages 7-8): Lan Wang, Xia Gao, Peng Gao, Weiwei Deng, Peng Yu, Jinjing Ma, Jinhai Guo, Xinyu Wang, Hualing Cheng, Chenying Zhang, Chuanfei Yu, Xi Ma, Bingfeng Lv, Yang Lu, Taiping Shi, and Dalong Ma. Cell-based screening and validation of human novel genes associated with cell viability. SLAS Discovery, 11:369-376, Jun 2006. URL: https://doi.org/10.1177/1087057106286654, doi:10.1177/1087057106286654. This article has 30 citations and is from a peer-reviewed journal.