1. Phylogeny  
   Phosphatidylinositol 4‑phosphate 3‑kinase C2 domain‑containing subunit beta (PIK3C2B) is a member of the class II phosphoinositide 3‑kinases (PI3Ks), a subgroup within the larger PI3K family that is evolutionarily conserved across metazoans. Unlike class I PI3Ks, which function as heterodimers with regulatory subunits, class II enzymes exist as monomeric proteins and are characterized by their distinct domain organization that includes one or more C2 domains and a Phox (PX) domain. Evolutionary studies have placed the class II PI3Ks in a divergent branch of the kinome, clearly set apart from the well‐studied heterodimeric class I isoforms and the class III kinase Vps34. Orthologs of PIK3C2B have been identified in various higher eukaryotes, indicating that the fundamental architecture and core function of these kinases have been maintained from early metazoan evolution. The evolutionary relationships, as derived from comparative kinome analyses, suggest that class II enzymes such as PIK3C2B arose from a common ancestral gene that subsequently diverged in higher organisms to acquire specialized roles in intracellular lipid signaling and membrane trafficking (arcaro2000classiiphosphoinositide pages 14-14, yu2015differentialregulatoryfunctions pages 5-8).
2. Reaction Catalyzed  
   PIK3C2B catalyzes the transfer of a phosphate group from ATP to specific phosphoinositide substrates in a reaction that can be summarized as follows: ATP + phosphatidylinositol (or phosphatidylinositol 4‑phosphate) → ADP + phosphorylated phosphoinositide + H⁺. In this reaction, the enzyme preferentially phosphorylates phosphatidylinositol (PtdIns) and phosphatidylinositol 4‑phosphate (PtdIns4P), thereby generating 3‑phosphorylated products such as phosphatidylinositol 3‑phosphate (PtdIns3P) and/or phosphatidylinositol 3,4‑bisphosphate (PI(3,4)P₂). Notably, PIK3C2B does not phosphorylate phosphatidylinositol 4,5‑bisphosphate [PtdIns(4,5)P₂], which distinguishes it from class I PI3Ks that generate PtdIns(3,4,5)P₃. This selective catalytic activity indicates that the enzyme’s substrate preference is confined to PtdIns and PtdIns4P, with a higher catalytic efficiency toward PtdIns (beeton2000functionaldifferencesof pages 21-25, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5).
3. Cofactor Requirements  
   The catalytic activity of PIK3C2B is dependent on the presence of divalent metal ions, with Mg²⁺ being the primary cofactor required for enzymatic function. Mg²⁺ facilitates the proper coordination and positioning of ATP within the catalytic site, thereby stabilizing the transition state during the phosphate transfer reaction. This cofactor requirement is consistent with the biochemical properties observed in many phosphoinositide kinases and is essential for the efficient phosphorylation of its lipid substrates (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5).
4. Substrate Specificity  
   PIK3C2B exhibits a distinct substrate specificity that is integral to its biological function. The enzyme phosphorylates phosphatidylinositol (PtdIns) and phosphatidylinositol 4‑phosphate (PtdIns4P), with a marked preference for PtdIns as the primary substrate. This activity results in the generation of 3‑phosphorylated lipid products such as PtdIns3P and, under certain conditions, PI(3,4)P₂. Critically, PIK3C2B does not act upon phosphatidylinositol 4,5‑bisphosphate [PtdIns(4,5)P₂], a specificity that helps define its unique role within the PI3K family. The substrate recognition is governed by the enzyme’s catalytic domain and associated lipid‐binding regions, which dictate the selective binding and efficient phosphorylation of PtdIns and PtdIns4P (gozzelino2020pi(34)p2signalingin pages 3-5, beeton2000functionaldifferencesof pages 21-25, das1998complexinteractionsof pages 80-83).
5. Structure  
   PIK3C2B displays a modular structure typical of class II PI3Ks. Its architecture includes an extended N‑terminal region containing a proline‑rich motif that is thought to mediate protein‑protein interactions. Central to its function is the catalytic kinase domain, which is evolutionarily conserved and responsible for ATP binding and the transfer of a phosphate group to the lipid substrates. Adjacent to the kinase domain is a Phox homology (PX) domain that plays a critical role in binding phosphoinositides, thereby facilitating proper subcellular localization. Toward the C‑terminal end, the protein contains one or more C2 domains; these domains are involved in membrane association by binding to phospholipid membranes in a calcium‑independent manner, a feature that differentiates them from other C2 domains that require Ca²⁺. Moreover, structural studies and predictive models have suggested the existence of an autoinhibitory mechanism whereby the C‑terminal PX‑C2 module folds back onto the kinase domain, thereby modulating enzyme activity. Unlike class I PI3Ks, which require association with regulatory subunits, PIK3C2B functions as a monomer—a unique trait that is attributed to its complete domain organization including the proposed Ras‑binding region in the N‑terminal extension (kampyli2020investigationintothe pages 29-32, kampyli2020investigationintothe pages 32-35, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, das1998complexinteractionsof pages 113-117).
6. Regulation  
   The activity of PIK3C2B is finely regulated by multiple post‑translational modifications and protein–protein interactions. One of the key regulatory mechanisms is phosphorylation: phosphorylation at residue T279 by protein kinase N2 (PKN2) creates a binding site for inhibitory 14‑3‑3 proteins, which subsequently leads to cytoplasmic retention and a reduction in kinase activity. This phosphorylation event thereby serves as a molecular switch controlling the subcellular localization and activity of PIK3C2B. In addition, the enzyme is subject to polyubiquitination; specifically, ubiquitination at lysine 49 mediated by the E3 ubiquitin ligase TRIM27 results in catalytic inactivation. This modification serves as a negative regulatory mechanism, effectively downregulating the production of 3‑phosphorylated phosphoinositides. Furthermore, the autoinhibitory interaction involving the C‑terminal PX‑C2 module, which folds back onto the kinase domain, is an intrinsic regulatory feature that modulates substrate access and enzymatic activity. PIK3C2B is also activated downstream of cell surface receptor signaling, including receptor tyrosine kinases (RTKs) such as those for EGF and PDGF, and G protein–coupled receptors (GPCRs) that respond to ligands like lysophosphatidic acid (LPA) and sphingosine 1‑phosphate (S1P). These receptor-mediated signals integrate with the post‑translational modifications to provide a multi‑layered control over PIK3C2B’s function (kampyli2020investigationintothe pages 35-38, kampyli2020investigationintothe pages 38-40, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, yu2015differentialregulatoryfunctions pages 5-8).
7. Function  
   PIK3C2B is involved in several critical cellular processes through its enzymatic role in phosphoinositide metabolism. By phosphorylating PtdIns and PtdIns4P, PIK3C2B generates localized pools of 3‑phosphorylated phosphoinositides that serve as second messengers in cellular signaling pathways. One prominent function of PIK3C2B is its role in the regulation of mTORC1 signaling: the production of phosphatidylinositol 3,4‑bisphosphate at lysosomal membranes has been linked to the modulation of mTORC1 activity, contributing to the regulation of cellular anabolic processes and metabolic homeostasis. In addition, PIK3C2B plays a significant role in endocytosis and vesicular trafficking. Its localization at clathrin‑coated pits and early endosomes suggests that it participates in the internalization and recycling of membrane receptors, including those activated by growth factors such as EGF and PDGF. This function in membrane trafficking is crucial for the maintenance of cellular signaling and receptor turnover. Moreover, PIK3C2B contributes to the reorganization of the actin cytoskeleton and cell migration. It does so by regulating the activities of small Rho GTPases, including Rac and RhoA, which are integral to the formation of lamellipodia and other actin‑driven structures that facilitate cell movement. Beyond these roles, PIK3C2B is also implicated in the regulation of immune cell function; for example, it modulates the opening of the intermediate‑conductance calcium‑activated potassium channel KCa3.1 in T cells and mast cells, thereby influencing immune cell activation and cytokine production. In a pathological context, aberrant expression and deregulation of PIK3C2B have been linked to enhanced invasive and metastatic behaviors in several cancers, including ovarian, prostate, cervical cancers, and neuroblastoma (gozzelino2020pi(34)p2signalingin pages 3-5, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, arcaro2000classiiphosphoinositide pages 14-14, tariq2021strikingabalance pages 26-31).
8. Other Comments  
   Additional observations regarding PIK3C2B include its potential as a pharmacological target for therapeutic intervention, particularly in oncology. Experimental studies have identified compounds such as PI701 that selectively inhibit the kinase activity of PI3K‑C2β, thereby reducing its downstream pro‑tumorigenic signaling (gozzelino2020pi(34)p2signalingin pages 3-5). The enzyme’s involvement in receptor tyrosine kinase (RTK) signaling cascades—triggered by growth factors like EGF and PDGF—further highlights its relevance in pathways that drive cell proliferation, survival, and migration. Moreover, its role in the regulation of immune cell activity through ion channel modulation underscores its potential impact on inflammatory and allergic responses. The specific structural attributes of PIK3C2B, such as the presence of PX and C2 domains, render it distinct from the heterodimeric class I PI3Ks, suggesting that targeted inhibitors could be developed to modulate its activity selectively without affecting other PI3K isoforms. Such specificity is of particular interest given the involvement of PI3K signaling in a broad array of diseases, including cancer and metabolic disorders (yu2015differentialregulatoryfunctions pages 5-8, tariq2021strikingabalance pages 26-31).
9. References
10. Gozzelino, L., De Santis, M. C., Gulluni, F., Hirsch, E., & Martini, M. “Pi(3,4)p2 signaling in cancer and metabolism.” Frontiers in Oncology, Mar 2020, pages 3-5, doi:10.3389/fonc.2020.00360. (gozzelino2020pi(34)p2signalingin pages 3-5)
11. Akinleye, A., Avvaru, P., Furqan, M., Song, Y., & Liu, D. “Phosphatidylinositol 3-kinase (pi3k) inhibitors as cancer therapeutics.” Journal of Hematology & Oncology, Nov 2013, pages 2-5, doi:10.1186/1756-8722-6-88. (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5)
12. Isakoff, S. J., Cardozo, T., Andreev, J., Li, Z., Ferguson, K. M., Abagyan, R., Lemmon, M. A., Aronheim, A., & Skolnik, E. Y. “Identification and analysis of ph domain-containing targets of phosphatidylinositol 3-kinase using a novel in vivo assay in yeast.” The EMBO Journal, Sep 1998, pages 1-2, doi:10.1093/emboj/17.18.5374. (isakoff1998identificationandanalysis pages 1-2)
13. Chen, C., Hu, J., & Ling, K. “The role of primary cilia-associated phosphoinositide signaling in development.” Journal of Developmental Biology, Dec 2022, pages 1-3, doi:10.3390/jdb10040051. (chen2022theroleof pages 1-3)
14. Rajala, R. V. “Phosphoinositide 3-kinase signaling in the vertebrate retina.” Journal of Lipid Research, Jan 2010, pages 2-3, doi:10.1194/jlr.r000232. (rajala2010phosphoinositide3kinasesignaling pages 2-3)
15. Yu, X., Long, Y. C., & Shen, H.-M. “Differential regulatory functions of three classes of phosphatidylinositol and phosphoinositide 3-kinases in autophagy.” Autophagy, Oct 2015, pages 5-8, doi:10.1080/15548627.2015.1043076. (yu2015differentialregulatoryfunctions pages 5-8)
16. Tariq, K. & Luikart, B. W. “Striking a balance: pip2 and pip3 signaling in neuronal health and disease.” Exploration of neuroprotective therapy, Oct 2021, pages 26-31, doi:10.37349/ent.2021.00008. (tariq2021strikingabalance pages 26-31)
17. Arcaro, A., Zvelebil, M. J., Wallasch, C., Ullrich, A., Waterfield, M. D., & Domin, J. “Class II phosphoinositide 3-kinases are downstream targets of activated polypeptide growth factor receptors.” Molecular and Cellular Biology, Jun 2000, pages 14-14, doi:10.1128/mcb.20.11.3817-3830. (arcaro2000classiiphosphoinositide pages 14-14)
18. Nakadatsukui, K., Watanabe, N., Maehama, T., & Nozaki, T. “Phosphatidylinositol kinases and phosphatases in entamoeba histolytica.” Frontiers in Cellular and Infection Microbiology, Jun 2019, pages 6-8, doi:10.3389/fcimb.2019.00150. (nakadatsukui2019phosphatidylinositolkinasesand pages 6-8)

References

1. (gozzelino2020pi(34)p2signalingin pages 3-5): Luca Gozzelino, Maria Chiara De Santis, Federico Gulluni, Emilio Hirsch, and Miriam Martini. Pi(3,4)p2 signaling in cancer and metabolism. Frontiers in Oncology, Mar 2020. URL: https://doi.org/10.3389/fonc.2020.00360, doi:10.3389/fonc.2020.00360. This article has 76 citations and is from a peer-reviewed journal.
2. (kampyli2020investigationintothe pages 35-38): C Kampyli. Investigation into the cell biological roles of class ii pi3k-c2β. Unknown journal, 2020.
3. (kampyli2020investigationintothe pages 38-40): C Kampyli. Investigation into the cell biological roles of class ii pi3k-c2β. Unknown journal, 2020.
4. (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5): Akintunde Akinleye, Parthu Avvaru, Muhammad Furqan, Yongping Song, and Delong Liu. Phosphatidylinositol 3-kinase (pi3k) inhibitors as cancer therapeutics. Journal of Hematology & Oncology, 6:88-88, Nov 2013. URL: https://doi.org/10.1186/1756-8722-6-88, doi:10.1186/1756-8722-6-88. This article has 340 citations.
5. (beeton2000functionaldifferencesof pages 21-25): CA Beeton. Functional differences of class 1a pi 3’-kinase heterodimers. Unknown journal, 2000.
6. (das1998complexinteractionsof pages 80-83): P Das. Complex interactions of the domains of the p85 adaptor subunit of phosphoinositide 3-kinase. Unknown journal, 1998.
7. (isakoff1998identificationandanalysis pages 1-2): Steven J. Isakoff, Tim Cardozo, Julian Andreev, Zhai Li, Kathryn M. Ferguson, Ruben Abagyan, Mark A. Lemmon, Ami Aronheim, and Edward Y. Skolnik. Identification and analysis of ph domain-containing targets of phosphatidylinositol 3-kinase using a novel in vivo assay in yeast. The EMBO Journal, 17:5374-5387, Sep 1998. URL: https://doi.org/10.1093/emboj/17.18.5374, doi:10.1093/emboj/17.18.5374. This article has 443 citations.
8. (kampyli2020investigationintothe pages 29-32): C Kampyli. Investigation into the cell biological roles of class ii pi3k-c2β. Unknown journal, 2020.
9. (kampyli2020investigationintothe pages 32-35): C Kampyli. Investigation into the cell biological roles of class ii pi3k-c2β. Unknown journal, 2020.
10. (nakadatsukui2019phosphatidylinositolkinasesand pages 6-8): 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. (tariq2021strikingabalance pages 26-31): K. Tariq and Bryan W. Luikart. Striking a balance: pip2 and pip3 signaling in neuronal health and disease. Exploration of neuroprotective therapy, 1:86-100, Oct 2021. URL: https://doi.org/10.37349/ent.2021.00008, doi:10.37349/ent.2021.00008. This article has 47 citations.
12. (das1998complexinteractionsof pages 113-117): P Das. Complex interactions of the domains of the p85 adaptor subunit of phosphoinositide 3-kinase. Unknown journal, 1998.
13. (arcaro2000classiiphosphoinositide pages 14-14): Alexandre Arcaro, Marketa J. Zvelebil, Christian Wallasch, Axel Ullrich, Michael D. Waterfield, and Jan Domin. Class ii phosphoinositide 3-kinases are downstream targets of activated polypeptide growth factor receptors. Molecular and Cellular Biology, 20:3817-3830, Jun 2000. URL: https://doi.org/10.1128/mcb.20.11.3817-3830.2000, doi:10.1128/mcb.20.11.3817-3830.2000. This article has 240 citations and is from a domain leading peer-reviewed journal.
14. (chen2022theroleof pages 1-3): 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.
15. (rajala2010phosphoinositide3kinasesignaling pages 2-3): R. V. Rajala. Phosphoinositide 3-kinase signaling in the vertebrate retina. Journal of Lipid Research, 51:22-4, Jan 2010. URL: https://doi.org/10.1194/jlr.r000232, doi:10.1194/jlr.r000232. This article has 51 citations and is from a peer-reviewed journal.
16. (yu2015differentialregulatoryfunctions pages 5-8): Xinlei Yu, Yun Chau Long, and Han-Ming Shen. Differential regulatory functions of three classes of phosphatidylinositol and phosphoinositide 3-kinases in autophagy. Autophagy, 11:1711-1728, Oct 2015. URL: https://doi.org/10.1080/15548627.2015.1043076, doi:10.1080/15548627.2015.1043076. This article has 230 citations and is from a domain leading peer-reviewed journal.