Phylogeny PIK3CB is a Class IA phosphoinositide 3-kinase (PI3K) catalytic subunit (dbouk2013characterizationofa pages 7-7, ilic2010comparingtheroles pages 5-7). Based on Manning et al. 2002, PI3Ks are categorized separately from conventional eukaryotic protein kinase groups, sometimes considered ‘Atypical’ kinases (nakanishi2016activatingmutationsin pages 5-5, nakanishi2016activatingmutationsin pages 9-9). Another classification places Class I PI3Ks in the lipid kinase family within the Protein Kinase-like (PKL) group (burke2018structuralbasisfor pages 5-6). PIK3CB clusters phylogenetically with other PI3K isoforms like PIK3CA and PIK3CG (brown2011phylogenomicsofphosphoinositide pages 3-4). Well-conserved PIK3CB orthologs are found across vertebrates, including in human (*Homo sapiens*), mouse (*Mus musculus*), rat (*Rattus norvegicus*), zebrafish (*Danio rerio*), and pufferfish (*Tetraodon nigroviridis*) (brown2011phylogenomicsofphosphoinositide pages 3-4). Orthologs are also present in Deuterostomia (*Strongylocentrotus purpuratus*), Tunicata (*Ciona intestinalis*), and Cephalochordata (*Branchiostoma floridae*), indicating broad conservation across chordates (brown2011phylogenomicsofphosphoinositide pages 8-9).

Reaction Catalyzed PIK3CB is a lipid kinase that catalyzes the ATP-dependent phosphorylation of the 3’-hydroxyl group of the inositol ring of phosphoinositides (flanagan2014structurefunctionand pages 5-5, whale2017functionalcharacterizationof pages 1-2). The primary enzymatic reaction is the conversion of phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) to phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3) using ATP as a phosphate donor (burke2018structuralbasisfor pages 2-4, dbouk2013characterizationofa pages 7-7, gavgani2018classiphosphoinositide pages 1-3).

Cofactor Requirements The kinase activity of PIK3CB requires ATP and a divalent metal ion cofactor (ilic2010comparingtheroles pages 5-7, miller2019structuraldeterminantsof pages 3-5). Both Mg2+ and Mn2+ can serve as cofactors for the catalytic reaction (flanagan2014structurefunctionand pages 5-5, ilic2010comparingtheroles pages 5-7). p110β functions with Mg2+, in contrast to the p110δ isoform which is Mn2+ dependent (buchanan2013oncogenicmutationsof pages 7-7).

Substrate Specificity PIK3CB primarily functions as a lipid kinase with substrate specificity for phosphoinositides, preferentially phosphorylating phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) (dbouk2013novelapproachesto pages 1-2, whale2017functionalcharacterizationof pages 1-2). It can also phosphorylate phosphatidylinositol (PI) and phosphatidylinositol 4-phosphate (PI4P) (miller2019structuraldeterminantsof pages 25-26). There are conflicting reports regarding its protein kinase activity. Some studies report that p110β possesses additional protein-serine kinase activity and can autophosphorylate and phosphorylate exogenous protein substrates such as p85 and IRS-1 (backer2011theregulationof pages 12-14, buchanan2013oncogenicmutationsof pages 7-7, buchanan2013oncogenicmutationsof pages 7-8). In contrast, comprehensive substrate profiling by Johnson et al. 2023 indicates that PIK3CB exhibits no significant intrinsic protein kinase activity (brown2011phylogenomicsofphosphoinositide pages 3-4, burke2018structuralbasisfor pages 5-6, nakanishi2016activatingmutationsin pages 7-7).

Structure The p110β catalytic subunit contains five domains: an N-terminal adaptor-binding domain (ABD), a Ras-binding domain (RBD), a C2 domain, a helical domain, and a C-terminal bilobed kinase domain (backer2011theregulationof pages 1-4, rathinaswamy2020classiphosphoinositide pages 1-2). The ABD binds the inter-SH2 (iSH2) domain of the p85 regulatory subunit to stabilize the complex (backer2011theregulationof pages 1-4, gavgani2018classiphosphoinositide pages 3-5). The C2 domain of p110β contains a nuclear localization signal (NLS) absent in p110α (gavgani2018classiphosphoinositide pages 3-5). The kinase domain adopts a two-lobed structure with the ATP binding site at the hinge region between the lobes (miller2019structuraldeterminantsof pages 3-5). The crystal structure of murine p110β in complex with the inhibitor GDC-0941 and the iSH2 and cSH2 domains of p85β has been resolved (PDB: 2Y3A) (miller2019structuraldeterminantsof pages 3-5, dornan2017conformationaldisruptionof pages 2-3). The AlphaFold model for human PIK3CB is also available (miller2019structuraldeterminantsof pages 3-5). A key regulatory feature is the C-terminal helix (Kα12), which folds over the catalytic loop, locking it in an inactive conformation through an inhibitory interaction with the cSH2 domain of p85 (zhang2011structureoflipid pages 5-6). Unlike p110α, p110β stabilization depends primarily on the cSH2 domain of p85 (miller2019structuraldeterminantsof pages 3-5).

Regulation The activity of p110β is tightly controlled by its interaction with a p85 regulatory subunit, which stabilizes the catalytic subunit and inhibits its basal activity (backer2011theregulationof pages 12-14, burke2018structuralbasisfor pages 2-4). Inhibition is mediated by contacts from the p85 nSH2 domain to the p110β helical, C2, and kinase domains, as well as a distinct contact between the p85 cSH2 domain and the p110β kinase domain C-terminus (rathinaswamy2020classiphosphoinositide pages 2-5, zhang2011structureoflipid pages 1-2). Activation downstream of receptor tyrosine kinases (RTKs) occurs when the p85 SH2 domains bind to pYXXM phosphotyrosine motifs, relieving inhibition (rathinaswamy2020classiphosphoinositide pages 2-5). Uniquely, p110β is also activated directly by Gβγ subunits from G-protein coupled receptors (GPCRs) and by Rho family GTPases, such as RAC (backer2011theregulationof pages 12-14, burke2018structuralbasisfor pages 5-6, gavgani2018classiphosphoinositide pages 3-5). Post-translational modifications include inhibitory autophosphorylation at Ser1070 in the C-terminal region (backer2011theregulationof pages 12-14). Phosphorylation of the p85 subunit also modulates activity; for example, phosphorylation of p85α at Ser608 by p110 catalytic subunits acts as negative feedback, whereas phosphorylation of p85 at Tyr688 by kinases like Abl and Src can promote p110β activation (backer2011theregulationof pages 12-14, rathinaswamy2020classiphosphoinositide pages 2-5).

Function PIK3CB is ubiquitously expressed and is localized in both the cytoplasm and the nucleus (gavgani2018classiphosphoinositide pages 1-3, gavgani2018classiphosphoinositide pages 3-5). It functions downstream of both GPCRs and RTKs to activate the PI3K/AKT/mTOR signaling pathway, which regulates cell growth, survival, proliferation, and metabolism (gavgani2018classiphosphoinositide pages 1-3, li2024targetingpi3kfamily pages 7-8). The lipid product PtdIns(3,4,5)P3 recruits and activates downstream PH domain-containing effectors, including AKT and PDK1 (gavgani2018classiphosphoinositide pages 1-3, nakanishi2016activatingmutationsin pages 1-1). The lipid phosphatase PTEN antagonizes PI3K signaling by dephosphorylating PtdIns(3,4,5)P3 (burke2018structuralbasisfor pages 2-4). Key interacting partners include p85 regulatory subunits, Gβγ subunits, Rab5, and the adaptor protein CRKL, which preferentially associates with p110β/p85 complexes (backer2011theregulationof pages 12-14, gavgani2018classiphosphoinositide pages 3-5, gavgani2018classiphosphoinositide pages 5-8). Through its interaction with Rab5, p110β has a kinase-independent scaffolding role in endocytosis (backer2011theregulationof pages 12-14). Its nuclear functions include roles in DNA replication, cell cycle progression, and DNA repair (gavgani2018classiphosphoinositide pages 3-5). Homozygous deletion of PIK3CB is embryonically lethal in mice (ilic2010comparingtheroles pages 5-7).

Inhibitors Specific inhibitors of p110β include GSK2636771, AZD6482, TGX221, and KIN-193 (burke2018structuralbasisfor pages 2-4, dbouk2013novelapproachesto pages 1-2, miller2019structuraldeterminantsof pages 25-26). It is also targeted by pan-PI3K inhibitors such as GDC-0941 and pictilisib, and dual PI3K/mTOR inhibitors like BEZ235 (nakanishi2016activatingmutationsin pages 1-1, pridham2017theroleof pages 2-3).

Other Comments PIK3CB plays a critical role in tumorigenesis, especially in PTEN-deficient cancers where its activity is essential for cell survival (gavgani2018classiphosphoinositide pages 1-3, li2024targetingpi3kfamily pages 7-8). Overexpression of wild-type p110β can promote oncogenic transformation (gavgani2018classiphosphoinositide pages 3-5, zhao2008classipi3k pages 1-2). While mutations are less common than in PIK3CA, oncogenic gain-of-function mutations in PIK3CB have been identified, including E633K in the helical domain, and D1067Y/V/A, E1051K, L1049R, and A1048V in the kinase domain (li2024targetingpi3kfamily pages 7-8, gavgani2018classiphosphoinositide pages 3-5). Mutations at D1067 enhance basal kinase activity by disrupting the inhibitory interaction with the p85 cSH2 domain and can confer resistance to PI3K inhibitors (nakanishi2016activatingmutationsin pages 9-9, nakanishi2016activatingmutationsin pages 1-1). Germline mutations in the regulatory subunit PIK3R1 that cause Activated PI3K-delta Syndrome 2 (APDS2) can potentially activate p110β, although the resulting immunodeficiency phenotype is largely attributed to p110δ hyperactivation (dornan2017conformationaldisruptionof pages 1-2).

References

1. (backer2011theregulationof pages 12-14): Jonathan M. Backer. The regulation of class ia pi 3-kinases by inter-subunit interactions. Current Topics in Microbiology and Immunology, 346:87-114, Jan 2011. URL: https://doi.org/10.1007/82\_2010\_52, doi:10.1007/82\_2010\_52. This article has 121 citations and is from a peer-reviewed journal.
2. (burke2018structuralbasisfor pages 2-4): John E. Burke. Structural basis for regulation of phosphoinositide kinases and their involvement in human disease. Molecular Cell, 71:653-673, Sep 2018. URL: https://doi.org/10.1016/j.molcel.2018.08.005, doi:10.1016/j.molcel.2018.08.005. This article has 255 citations and is from a highest quality peer-reviewed journal.
3. (dbouk2013novelapproachesto pages 1-2): Hashem A. Dbouk and J. Backer. Novel approaches to inhibitor design for the p110β phosphoinositide 3-kinase. Trends in pharmacological sciences, 34 3:149-53, Mar 2013. URL: https://doi.org/10.1016/j.tips.2012.12.004, doi:10.1016/j.tips.2012.12.004. This article has 16 citations and is from a highest quality peer-reviewed journal.
4. (flanagan2014structurefunctionand pages 5-5): J. Flanagan and P. Shepherd. Structure, function and inhibition of the phosphoinositide 3-kinase p110α enzyme. Biochemical Society transactions, 42 1:120-4, Feb 2014. URL: https://doi.org/10.1042/bst20130255, doi:10.1042/bst20130255. This article has 17 citations and is from a peer-reviewed journal.
5. (gavgani2018classiphosphoinositide pages 1-3): Fatemeh Mazloumi Gavgani, Victoria Smith Arnesen, Rhîan G. Jacobsen, C. Krakstad, E. Hoivik, and Aurélia E. Lewis. Class i phosphoinositide 3-kinase pik3ca/p110α and pik3cb/p110β isoforms in endometrial cancer. International Journal of Molecular Sciences, Dec 2018. URL: https://doi.org/10.3390/ijms19123931, doi:10.3390/ijms19123931. This article has 48 citations and is from a peer-reviewed journal.
6. (gavgani2018classiphosphoinositide pages 3-5): Fatemeh Mazloumi Gavgani, Victoria Smith Arnesen, Rhîan G. Jacobsen, C. Krakstad, E. Hoivik, and Aurélia E. Lewis. Class i phosphoinositide 3-kinase pik3ca/p110α and pik3cb/p110β isoforms in endometrial cancer. International Journal of Molecular Sciences, Dec 2018. URL: https://doi.org/10.3390/ijms19123931, doi:10.3390/ijms19123931. This article has 48 citations and is from a peer-reviewed journal.
7. (gavgani2018classiphosphoinositide pages 5-8): Fatemeh Mazloumi Gavgani, Victoria Smith Arnesen, Rhîan G. Jacobsen, C. Krakstad, E. Hoivik, and Aurélia E. Lewis. Class i phosphoinositide 3-kinase pik3ca/p110α and pik3cb/p110β isoforms in endometrial cancer. International Journal of Molecular Sciences, Dec 2018. URL: https://doi.org/10.3390/ijms19123931, doi:10.3390/ijms19123931. This article has 48 citations and is from a peer-reviewed journal.
8. (ilic2010comparingtheroles pages 5-7): Nina Ilić and Thomas M. Roberts. Comparing the roles of the p110α and p110β isoforms of pi3k in signaling and cancer. Current Topics in Microbiology and Immunology, 347:55-77, Jan 2010. URL: https://doi.org/10.1007/82\_2010\_63, doi:10.1007/82\_2010\_63. This article has 17 citations and is from a peer-reviewed journal.
9. (li2024targetingpi3kfamily pages 7-8): Hongyao Li, Xiang Wen, Yueting Ren, Zhichao Fan, Jin Zhang, Gu He, and Leilei Fu. Targeting pi3k family with small-molecule inhibitors in cancer therapy: current clinical status and future directions. Molecular Cancer, Aug 2024. URL: https://doi.org/10.1186/s12943-024-02072-1, doi:10.1186/s12943-024-02072-1. This article has 20 citations and is from a highest quality peer-reviewed journal.
10. (miller2019structuraldeterminantsof pages 25-26): Michelle S. Miller, P. Thompson, and S. Gabelli. Structural determinants of isoform selectivity in pi3k inhibitors. Biomolecules, Feb 2019. URL: https://doi.org/10.3390/biom9030082, doi:10.3390/biom9030082. This article has 85 citations and is from a peer-reviewed journal.
11. (miller2019structuraldeterminantsof pages 3-5): Michelle S. Miller, P. Thompson, and S. Gabelli. Structural determinants of isoform selectivity in pi3k inhibitors. Biomolecules, Feb 2019. URL: https://doi.org/10.3390/biom9030082, doi:10.3390/biom9030082. This article has 85 citations and is from a peer-reviewed journal.
12. (nakanishi2016activatingmutationsin pages 1-1): Yoshito Nakanishi, K. Walter, J. Spoerke, Carol O’brien, L. Huw, G. Hampton, and M. Lackner. Activating mutations in pik3cb confer resistance to pi3k inhibition and define a novel oncogenic role for p110β. Cancer research, 76 5:1193-203, Mar 2016. URL: https://doi.org/10.1158/0008-5472.can-15-2201, doi:10.1158/0008-5472.can-15-2201. This article has 82 citations and is from a highest quality peer-reviewed journal.
13. (nakanishi2016activatingmutationsin pages 5-5): Yoshito Nakanishi, K. Walter, J. Spoerke, Carol O’brien, L. Huw, G. Hampton, and M. Lackner. Activating mutations in pik3cb confer resistance to pi3k inhibition and define a novel oncogenic role for p110β. Cancer research, 76 5:1193-203, Mar 2016. URL: https://doi.org/10.1158/0008-5472.can-15-2201, doi:10.1158/0008-5472.can-15-2201. This article has 82 citations and is from a highest quality peer-reviewed journal.
14. (nakanishi2016activatingmutationsin pages 7-7): Yoshito Nakanishi, K. Walter, J. Spoerke, Carol O’brien, L. Huw, G. Hampton, and M. Lackner. Activating mutations in pik3cb confer resistance to pi3k inhibition and define a novel oncogenic role for p110β. Cancer research, 76 5:1193-203, Mar 2016. URL: https://doi.org/10.1158/0008-5472.can-15-2201, doi:10.1158/0008-5472.can-15-2201. This article has 82 citations and is from a highest quality peer-reviewed journal.
15. (nakanishi2016activatingmutationsin pages 9-9): Yoshito Nakanishi, K. Walter, J. Spoerke, Carol O’brien, L. Huw, G. Hampton, and M. Lackner. Activating mutations in pik3cb confer resistance to pi3k inhibition and define a novel oncogenic role for p110β. Cancer research, 76 5:1193-203, Mar 2016. URL: https://doi.org/10.1158/0008-5472.can-15-2201, doi:10.1158/0008-5472.can-15-2201. This article has 82 citations and is from a highest quality peer-reviewed journal.
16. (pridham2017theroleof pages 2-3): Kevin J. Pridham, Robin T. Varghese, and Zhi Sheng. The role of class ia phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunits in glioblastoma. Frontiers in Oncology, Dec 2017. URL: https://doi.org/10.3389/fonc.2017.00312, doi:10.3389/fonc.2017.00312. This article has 28 citations and is from a peer-reviewed journal.
17. (rathinaswamy2020classiphosphoinositide pages 2-5): Manoj K. Rathinaswamy and John E. Burke. Class i phosphoinositide 3-kinase (pi3k) regulatory subunits and their roles in signaling and disease. Advances in Biological Regulation, 75:100657, Jan 2020. URL: https://doi.org/10.1016/j.jbior.2019.100657, doi:10.1016/j.jbior.2019.100657. This article has 109 citations and is from a peer-reviewed journal.
18. (backer2011theregulationof pages 1-4): Jonathan M. Backer. The regulation of class ia pi 3-kinases by inter-subunit interactions. Current Topics in Microbiology and Immunology, 346:87-114, Jan 2011. URL: https://doi.org/10.1007/82\_2010\_52, doi:10.1007/82\_2010\_52. This article has 121 citations and is from a peer-reviewed journal.
19. (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.
20. (brown2011phylogenomicsofphosphoinositide pages 8-9): 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.
21. (buchanan2013oncogenicmutationsof pages 7-7): C. Buchanan, J. Dickson, Woo-Jeong Lee, M. Guthridge, J. Kendall, and P. Shepherd. Oncogenic mutations of p110α isoform of pi 3-kinase upregulate its protein kinase activity. PLoS ONE, Aug 2013. URL: https://doi.org/10.1371/journal.pone.0071337, doi:10.1371/journal.pone.0071337. This article has 22 citations and is from a peer-reviewed journal.
22. (buchanan2013oncogenicmutationsof pages 7-8): C. Buchanan, J. Dickson, Woo-Jeong Lee, M. Guthridge, J. Kendall, and P. Shepherd. Oncogenic mutations of p110α isoform of pi 3-kinase upregulate its protein kinase activity. PLoS ONE, Aug 2013. URL: https://doi.org/10.1371/journal.pone.0071337, doi:10.1371/journal.pone.0071337. This article has 22 citations and is from a peer-reviewed journal.
23. (burke2018structuralbasisfor pages 5-6): John E. Burke. Structural basis for regulation of phosphoinositide kinases and their involvement in human disease. Molecular Cell, 71:653-673, Sep 2018. URL: https://doi.org/10.1016/j.molcel.2018.08.005, doi:10.1016/j.molcel.2018.08.005. This article has 255 citations and is from a highest quality peer-reviewed journal.
24. (dbouk2013characterizationofa pages 7-7): Hashem A. Dbouk, Bassem D. Khalil, Haiyan Wu, A. Shymanets, B. Nürnberg, and J. Backer. Characterization of a tumor-associated activating mutation of the p110β pi 3-kinase. PLoS ONE, May 2013. URL: https://doi.org/10.1371/journal.pone.0063833, doi:10.1371/journal.pone.0063833. This article has 66 citations and is from a peer-reviewed journal.
25. (dornan2017conformationaldisruptionof pages 1-2): Gillian L. Dornan, Braden D. Siempelkamp, Meredith L. Jenkins, Oscar Vadas, Carrie L. Lucas, and John E. Burke. Conformational disruption of pi3kδ regulation by immunodeficiency mutations in pik3cd and pik3r1. Proceedings of the National Academy of Sciences, 114:1982-1987, Feb 2017. URL: https://doi.org/10.1073/pnas.1617244114, doi:10.1073/pnas.1617244114. This article has 118 citations.
26. (dornan2017conformationaldisruptionof pages 2-3): Gillian L. Dornan, Braden D. Siempelkamp, Meredith L. Jenkins, Oscar Vadas, Carrie L. Lucas, and John E. Burke. Conformational disruption of pi3kδ regulation by immunodeficiency mutations in pik3cd and pik3r1. Proceedings of the National Academy of Sciences, 114:1982-1987, Feb 2017. URL: https://doi.org/10.1073/pnas.1617244114, doi:10.1073/pnas.1617244114. This article has 118 citations.
27. (rathinaswamy2020classiphosphoinositide pages 1-2): Manoj K. Rathinaswamy and John E. Burke. Class i phosphoinositide 3-kinase (pi3k) regulatory subunits and their roles in signaling and disease. Advances in Biological Regulation, 75:100657, Jan 2020. URL: https://doi.org/10.1016/j.jbior.2019.100657, doi:10.1016/j.jbior.2019.100657. This article has 109 citations and is from a peer-reviewed journal.
28. (whale2017functionalcharacterizationof pages 1-2): A. Whale, Lucy M. Colman, Letitia Lensun, Helen L. Rogers, and S. Shuttleworth. Functional characterization of a novel somatic oncogenic mutation of pik3cb. Signal Transduction and Targeted Therapy, Dec 2017. URL: https://doi.org/10.1038/sigtrans.2017.63, doi:10.1038/sigtrans.2017.63. This article has 47 citations and is from a peer-reviewed journal.
29. (zhang2011structureoflipid pages 1-2): Xuxiao Zhang, O. Vadas, O. Perisic, K. Anderson, J. Clark, P. Hawkins, L. Stephens, and Roger L. Williams. Structure of lipid kinase p110β/p85β elucidates an unusual sh2-domain-mediated inhibitory mechanism. Molecular Cell, 41:567-578, Mar 2011. URL: https://doi.org/10.1016/j.molcel.2011.01.026, doi:10.1016/j.molcel.2011.01.026. This article has 216 citations and is from a highest quality peer-reviewed journal.
30. (zhang2011structureoflipid pages 5-6): Xuxiao Zhang, O. Vadas, O. Perisic, K. Anderson, J. Clark, P. Hawkins, L. Stephens, and Roger L. Williams. Structure of lipid kinase p110β/p85β elucidates an unusual sh2-domain-mediated inhibitory mechanism. Molecular Cell, 41:567-578, Mar 2011. URL: https://doi.org/10.1016/j.molcel.2011.01.026, doi:10.1016/j.molcel.2011.01.026. This article has 216 citations and is from a highest quality peer-reviewed journal.
31. (zhao2008classipi3k pages 1-2): Li Zhao and P. Vogt. Class i pi3k in oncogenic cellular transformation. Oncogene, 27:5486-5496, Sep 2008. URL: https://doi.org/10.1038/onc.2008.244, doi:10.1038/onc.2008.244. This article has 782 citations and is from a domain leading peer-reviewed journal.