1. Phylogeny  
   PIK3CD, which encodes the p110δ catalytic subunit of phosphatidylinositol 3‐kinases (PI3Ks), is a member of the class IA PI3K family that is highly conserved among eukaryotes. Orthologs of PIK3CD have been identified across vertebrate species, and its evolutionary origins can be traced back to the ancient kinase superfamily that emerged early in eukaryotic evolution (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, bilanges2019pi3kisoformsin pages 1-2). Within the kinome, the class I PI3Ks are grouped together based on their shared catalytic mechanism and modular domain architecture, and p110δ itself is distinct due to its predominant expression in leukocytes. Unlike the ubiquitously expressed p110α and p110β, p110δ is mostly confined to cells of the immune system, a specialization that is reflected in its gene regulation and functional interactions (fruman2017thepi3kpathway pages 2-4). Phylogenetically, p110δ has diverged from its other class IA counterparts yet retains a structurally conserved core that includes an adaptor-binding domain, Ras-binding domain, C2 domain, helical domain, and catalytic kinase domain. These features have been maintained throughout evolution, underscoring its critical role in both cell signaling and immune function (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, bilanges2019pi3kisoformsin pages 1-2). The close evolutionary relationship with other class I PI3Ks also emphasizes that p110δ forms part of a regulatory network that includes ancient components such as PTEN, PDK1, and AKT, which together constitute a core signaling module conserved from yeast to humans (fruman2017thepi3kpathway pages 2-4).
2. Reaction Catalyzed  
   PIK3CD catalyzes the ATP-dependent phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) at the D3 position of the inositol ring to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3), with concomitant formation of ADP and the release of a proton. This reaction is essential to generate PIP3, a key lipid second messenger that recruits pleckstrin homology (PH) domain-containing proteins to the plasma membrane, thereby instigating a cascade of intracellular signal transduction events (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, yang2015idelalisibfirstinclasspi3k pages 10-12). In its simplest form, the reaction can be represented as: ATP + PIP2 → ADP + PIP3 + H⁺. This catalytic process is central to the function of PI3Kδ in mediating receptor-initiated cellular responses such as proliferation, survival, and migration (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2).
3. Cofactor Requirements  
   The activity of the p110δ subunit is strictly dependent on the presence of divalent cations, with magnesium ions (Mg²⁺) being the principal cofactor required for catalysis. Mg²⁺ acts to stabilize the binding of ATP in the kinase active site and facilitates the phosphoryl transfer reaction that converts PIP2 to PIP3 (uddin2025phosphatidylinositolkinasesin pages 1-3, zhong2013mir30asuppressescell pages 10-10). The requirement for Mg²⁺ is common to many protein and lipid kinases, and in the case of PI3Kδ, it ensures the proper orientation and reactivity of ATP within the catalytic cleft. Consequently, any disruption in the availability of Mg²⁺ can lead to a marked decrease in the enzymatic efficiency of PI3Kδ (uddin2025phosphatidylinositolkinasesin pages 1-3).
4. Substrate Specificity  
   PI3Kδ exhibits a high degree of substrate specificity, preferentially utilizing phosphatidylinositol 4,5-bisphosphate (PIP2) as its substrate in a membrane environment. The enzyme phosphorylates the 3′-hydroxyl group on the inositol ring of PIP2 to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3), a pivotal second messenger that orchestrates the recruitment of downstream effectors possessing PH domains, such as AKT and PDPK1 (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, dornan2019definingthemolecular pages 71-74, yang2015idelalisibfirstinclasspi3k pages 10-12). The substrate specificity is dictated not only by the chemical structure of PIP2 but also by the lipid environment provided by the plasma membrane, which positions the substrate correctly for interaction with the catalytic site. This selective catalytic activity underlies the ability of PI3Kδ to generate spatially and temporally restricted PIP3 pools, thereby precisely modulating downstream signaling pathways in immune cells (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2).
5. Structure  
   The p110δ catalytic subunit encoded by PIK3CD is organized into a series of well-defined structural domains that confer both catalytic function and regulatory control. At the extreme N-terminus, the adaptor-binding domain (ABD) mediates the constitutive interaction with the p85 regulatory subunit, a critical association that stabilizes p110δ in an autoinhibited conformation under resting conditions (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5, burke2018structuralbasisfor pages 4-5). Immediately following the ABD is the Ras-binding domain (RBD), which facilitates binding to GTP-bound Ras proteins, thereby contributing to the recruitment of the enzyme to membrane compartments upon receptor activation (dornan2019definingthemolecular pages 21-26, lucas2016pi3kδandprimary pages 30-31). Centrally located is the C2 domain, which is implicated in membrane binding by interacting with phospholipids, and this interaction helps to orient the enzyme’s catalytic core relative to its substrate (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). Following the C2 domain is the helical domain, which plays a significant role in intramolecular regulatory interactions and contributes to the formation of inhibitory interfaces with the regulatory subunit (burke2018structuralbasisfor pages 4-5, dornan2019definingthemolecular pages 21-26). The final and largest region is the kinase domain, which is subdivided into an N-lobe and a C-lobe; the N-lobe contains β sheets that contribute to ATP binding, while the C-lobe houses the catalytic residues that facilitate phosphoryl transfer (dornan2019definingthemolecular pages 21-26, lucas2016pi3kδandprimary pages 30-31). Within the kinase domain, key features such as the activation loop, hydrophobic spine, and C-helix are critical for catalysis and conformational regulation; these structural elements are conserved across class IA PI3Ks and are essential for coordinating the binding of ATP and substrate (burke2018structuralbasisfor pages 6-7, dornan2019definingthemolecular pages 30-33). High-resolution crystal structures as well as biophysical studies using hydrogen-deuterium exchange mass spectrometry (HDX-MS) have further elucidated the dynamic conformational changes of p110δ that occur upon activation, reinforcing the importance of its modular architecture in controlling enzyme activity (dornan2017conformationaldisruptionof pages 1-2, dornan2019definingthemolecular pages 21-26).
6. Regulation  
   The regulation of PI3Kδ is achieved through multiple interconnected mechanisms that ensure its activity is tightly controlled in response to external signals. In quiescent cells, the p110δ catalytic subunit is maintained in an inhibited state through its constitutive association with the p85 regulatory subunit; the SH2 domains of p85 interact with specific regions of p110δ, including the C2, helical, and kinase domains, thereby imposing an intramolecular “brake” on its catalytic activity (dornan2017conformationaldisruptionof pages 1-2, dornan2017conformationaldisruptionof pages 4-4). Upon stimulation through receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), or antigen receptors, phosphorylated tyrosine motifs on these receptors or associated adaptor proteins bind to the SH2 domains of the p85 subunit. This event disrupts the inhibitory contacts and leads to the translocation of the p110δ/p85 complex to the plasma membrane where substrate PIP2 is concentrated (lucas2016pi3kδandprimary pages 6-8, okkenhaug2013signalingbythe pages 6-8). In addition to receptor-mediated regulation, direct binding of Ras-GTP to the Ras-binding domain (RBD) of p110δ further contributes to its activation by promoting productive conformational changes that enhance catalytic efficiency (dornan2019definingthemolecular pages 71-74, bilanges2019pi3kisoformsin pages 7-8). Although the detailed profile of post-translational modifications for p110δ is less extensively characterized, phosphorylation events—both autophosphorylation and phosphorylation by upstream kinases—are known to modulate the activity of other related kinases, suggesting a similar regulatory paradigm may exist for PI3Kδ (dornan2017conformationaldisruptionof pages 1-2, lucas2016pi3kδandprimary pages 6-8). Disruption of these finely tuned regulatory mechanisms, for instance by gain-of-function mutations that impair inhibitory interactions, leads to aberrant PI3Kδ activation and is associated with primary immunodeficiency disorders such as activated PI3Kδ syndrome (APDS) (dornan2017conformationaldisruptionof pages 1-2, bier2019activatingmutationsin pages 1-3).
7. Function  
   The primary function of p110δ is to generate lipid second messengers that are crucial for propagating intracellular signals in immune cells. Due to its predominant expression in leukocytes, PI3Kδ plays an indispensable role in the development and function of both B and T lymphocytes. In B cells, p110δ is a key mediator of B-cell receptor (BCR) signaling, contributing to cell proliferation, survival, migration, and differentiation. Specifically, upon engagement of the BCR and associated co-receptors such as CD40 and IL-4 receptor, activated PI3Kδ catalyzes the conversion of PIP2 to PIP3, which in turn recruits downstream effectors including AKT and PDPK1 to the membrane. This recruitment facilitates a cascade of events that promote B-cell proliferation, mediate antibody class switching, and support antigen presentation functions (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, lucas2016pi3kδandprimary pages 30-31). In T cells, PI3Kδ participates in antigen receptor signalling that governs cell activation, differentiation, and survival, thereby influencing the overall immune response. Moreover, PI3Kδ contributes to chemotaxis by regulating the reorganization of the actin cytoskeleton through its production of PIP3, which recruits key signaling molecules to the leading edge of migrating cells (dornan2019definingthemolecular pages 33-37, olayinkaadefemi2020thefunctionof pages 65-71). Through these mechanisms, p110δ integrates extracellular signals received from the immune synapse and other receptor complexes into appropriate intracellular responses. The critical role of PI3Kδ in mediating immune cell activation and migration places it at the core of both innate and adaptive immune responses, with dysregulation contributing to immunodeficiency, autoimmunity, and lymphoid malignancies (lucas2016pi3kδandprimary pages 30-31, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5).
8. Other Comments  
   Given its central role in immune cell signaling, PI3Kδ has emerged as a prominent therapeutic target. Selective inhibitors, such as idelalisib and other compounds within the same chemical class, have been developed to specifically target the p110δ isoform. These inhibitors are clinically employed in the treatment of various B-cell malignancies, including chronic lymphocytic leukemia, small lymphocytic lymphoma, and follicular lymphoma, where aberrant PI3Kδ signaling contributes to disease pathogenesis (yang2015idelalisibfirstinclasspi3k pages 10-12, stark2015pi3kinhibitorsin pages 17-18). In addition, hyperactivating mutations in PIK3CD, which lead to activated PI3Kδ syndrome (APDS), result in gain-of-function phenotypes that drive immune dysregulation, lymphoproliferation, and increased susceptibility to infections. These mutations serve as both diagnostic markers and targets for therapeutic intervention, with ongoing research aimed at optimizing inhibitor selectivity and reducing associated toxicities (bier2019activatingmutationsin pages 1-3, thouenon2021activatedpi3kinasedelta pages 1-3, takeda2017novelpik3cdmutations pages 10-13). Furthermore, structural and functional studies employing techniques such as HDX-MS have provided detailed insights into the conformational changes induced by disease-associated mutations, thereby informing rational drug design strategies (takeda2017novelpik3cdmutations pages 16-18, dornan2019definingthemolecular pages 141-144). Collectively, these findings underscore the importance of PI3Kδ not only in normal immune physiology but also in various pathological conditions including immunodeficiencies and hematologic malignancies, and they continue to drive the development of targeted therapies to modulate its activity effectively (stark2015pi3kinhibitorsin pages 8-9, yang2015idelalisibfirstinclasspi3k pages 10-12).

References

1. (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.
2. (bilanges2019pi3kisoformsin pages 7-8): Benoit Bilanges, York Posor, and Bart Vanhaesebroeck. Pi3k isoforms in cell signalling and vesicle trafficking. Nature Reviews Molecular Cell Biology, 20:515-534, May 2019. URL: https://doi.org/10.1038/s41580-019-0129-z, doi:10.1038/s41580-019-0129-z. This article has 490 citations and is from a domain leading peer-reviewed journal.
3. (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 117 citations.
4. (dornan2017conformationaldisruptionof pages 4-4): 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 117 citations.
5. (dornan2019definingthemolecular pages 21-26): GL Dornan. Defining the molecular mechanisms mediating class ia phosphoinositide 3-kinase (pi3k) regulation and their role in human disease. Unknown journal, 2019.
6. (dornan2019definingthemolecular pages 30-33): GL Dornan. Defining the molecular mechanisms mediating class ia phosphoinositide 3-kinase (pi3k) regulation and their role in human disease. Unknown journal, 2019.
7. (dornan2019definingthemolecular pages 33-37): GL Dornan. Defining the molecular mechanisms mediating class ia phosphoinositide 3-kinase (pi3k) regulation and their role in human disease. Unknown journal, 2019.
8. (dornan2019definingthemolecular pages 71-74): GL Dornan. Defining the molecular mechanisms mediating class ia phosphoinositide 3-kinase (pi3k) regulation and their role in human disease. Unknown journal, 2019.
9. (lucas2016pi3kδandprimary pages 30-31): Carrie L. Lucas, Anita Chandra, Sergey Nejentsev, Alison M. Condliffe, and Klaus Okkenhaug. Pi3kδ and primary immunodeficiencies. Nature Reviews Immunology, 16:702-714, Sep 2016. URL: https://doi.org/10.1038/nri.2016.93, doi:10.1038/nri.2016.93. This article has 352 citations and is from a highest quality peer-reviewed journal.
10. (lucas2016pi3kδandprimary pages 6-8): Carrie L. Lucas, Anita Chandra, Sergey Nejentsev, Alison M. Condliffe, and Klaus Okkenhaug. Pi3kδ and primary immunodeficiencies. Nature Reviews Immunology, 16:702-714, Sep 2016. URL: https://doi.org/10.1038/nri.2016.93, doi:10.1038/nri.2016.93. This article has 352 citations and is from a highest quality peer-reviewed journal.
11. (okkenhaug2013signalingbythe pages 6-8): Klaus Okkenhaug. Signaling by the phosphoinositide 3-kinase family in immune cells. Annual Review of Immunology, 31:675-704, Mar 2013. URL: https://doi.org/10.1146/annurev-immunol-032712-095946, doi:10.1146/annurev-immunol-032712-095946. This article has 521 citations and is from a highest quality peer-reviewed journal.
12. (olayinkaadefemi2020thefunctionof pages 65-71): F. Olayinka-Adefemi, Chukwunonso Onyilagha, N. Jayachandran, Sen Hou, P. Jia, Jude E. Uzonna, and A. Marshall. The function of phosphatidylinositol 3-kinase delta (pi3kδ) enzyme in protective immunity to trypanosoma congolense infection in mice: the role of regulatory b cells. The Journal of Immunology, May 2020. URL: https://doi.org/10.4049/jimmunol.204.supp.82.39, doi:10.4049/jimmunol.204.supp.82.39. This article has 0 citations.
13. (stark2015pi3kinhibitorsin pages 17-18): Anne-Katrien Stark, Srividya Sriskantharajah, Edith M Hessel, and Klaus Okkenhaug. Pi3k inhibitors in inflammation, autoimmunity and cancer. Current Opinion in Pharmacology, 23:82-91, Aug 2015. URL: https://doi.org/10.1016/j.coph.2015.05.017, doi:10.1016/j.coph.2015.05.017. This article has 349 citations and is from a peer-reviewed journal.
14. (uddin2025phosphatidylinositolkinasesin pages 1-3): M Uddin. Phosphatidylinositol kinases in gtopdb v. 2025.1. Unknown journal, 2025.
15. (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2): 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.
16. (bier2019activatingmutationsin pages 1-3): Julia Bier, Geetha Rao, Kathryn Payne, Henry Brigden, Elise French, Simon J. Pelham, Anthony Lau, Helen Lenthall, Emily S.J. Edwards, Joanne M. Smart, Theresa S. Cole, Sharon Choo, Avni Y. Joshi, Roshini S. Abraham, Michael O’Sullivan, Kaan Boztug, Isabelle Meyts, Paul E. Gray, Lucinda J. Berglund, Peter Hsu, Melanie Wong, Steven M. Holland, Luigi D. Notarangelo, Gulbu Uzel, Cindy S. Ma, Robert Brink, Stuart G. Tangye, and Elissa K. Deenick. Activating mutations in pik3cd disrupt the differentiation and function of human and murine cd4+ t cells. Journal of Allergy and Clinical Immunology, 144:236-253, Jul 2019. URL: https://doi.org/10.1016/j.jaci.2019.01.033, doi:10.1016/j.jaci.2019.01.033. This article has 65 citations and is from a highest quality peer-reviewed journal.
17. (bilanges2019pi3kisoformsin pages 1-2): Benoit Bilanges, York Posor, and Bart Vanhaesebroeck. Pi3k isoforms in cell signalling and vesicle trafficking. Nature Reviews Molecular Cell Biology, 20:515-534, May 2019. URL: https://doi.org/10.1038/s41580-019-0129-z, doi:10.1038/s41580-019-0129-z. This article has 490 citations and is from a domain leading peer-reviewed journal.
18. (burke2018structuralbasisfor pages 4-5): JE Burke. Structural basis for regulation of phosphoinositide kinases and their involvement in human disease. Molecular cell, 71 5:653-673, Sep 2018. URL: https://doi.org/10.1016/j.molcel.2018.08.005, doi:10.1016/j.molcel.2018.08.005. This article has 254 citations and is from a highest quality peer-reviewed journal.
19. (burke2018structuralbasisfor pages 6-7): JE Burke. Structural basis for regulation of phosphoinositide kinases and their involvement in human disease. Molecular cell, 71 5:653-673, Sep 2018. URL: https://doi.org/10.1016/j.molcel.2018.08.005, doi:10.1016/j.molcel.2018.08.005. This article has 254 citations and is from a highest quality peer-reviewed journal.
20. (dornan2019definingthemolecular pages 141-144): GL Dornan. Defining the molecular mechanisms mediating class ia phosphoinositide 3-kinase (pi3k) regulation and their role in human disease. Unknown journal, 2019.
21. (stark2015pi3kinhibitorsin pages 8-9): Anne-Katrien Stark, Srividya Sriskantharajah, Edith M Hessel, and Klaus Okkenhaug. Pi3k inhibitors in inflammation, autoimmunity and cancer. Current Opinion in Pharmacology, 23:82-91, Aug 2015. URL: https://doi.org/10.1016/j.coph.2015.05.017, doi:10.1016/j.coph.2015.05.017. This article has 349 citations and is from a peer-reviewed journal.
22. (takeda2017novelpik3cdmutations pages 10-13): Andrew J. Takeda, Yu Zhang, Gillian L. Dornan, Braden D. Siempelkamp, Meredith L. Jenkins, Helen F. Matthews, Joshua J. McElwee, Weimin Bi, Filiz O. Seeborg, Helen C. Su, John E. Burke, and Carrie L. Lucas. Novel pik3cd mutations affecting n-terminal residues of p110δ cause activated pi3kδ syndrome (apds) in humans. Journal of Allergy and Clinical Immunology, 140:1152-1156.e10, Oct 2017. URL: https://doi.org/10.1016/j.jaci.2017.03.026, doi:10.1016/j.jaci.2017.03.026. This article has 80 citations and is from a highest quality peer-reviewed journal.
23. (takeda2017novelpik3cdmutations pages 16-18): Andrew J. Takeda, Yu Zhang, Gillian L. Dornan, Braden D. Siempelkamp, Meredith L. Jenkins, Helen F. Matthews, Joshua J. McElwee, Weimin Bi, Filiz O. Seeborg, Helen C. Su, John E. Burke, and Carrie L. Lucas. Novel pik3cd mutations affecting n-terminal residues of p110δ cause activated pi3kδ syndrome (apds) in humans. Journal of Allergy and Clinical Immunology, 140:1152-1156.e10, Oct 2017. URL: https://doi.org/10.1016/j.jaci.2017.03.026, doi:10.1016/j.jaci.2017.03.026. This article has 80 citations and is from a highest quality peer-reviewed journal.
24. (thouenon2021activatedpi3kinasedelta pages 1-3): Romane Thouenon, Nidia Moreno-Corona, Lucie Poggi, Anne Durandy, and Sven Kracker. Activated pi3kinase delta syndrome—a multifaceted disease. Frontiers in Pediatrics, Jun 2021. URL: https://doi.org/10.3389/fped.2021.652405, doi:10.3389/fped.2021.652405. This article has 32 citations and is from a peer-reviewed journal.
25. (yang2015idelalisibfirstinclasspi3k pages 10-12): Qingshan Yang, Prexy Modi, Terry Newcomb, Christophe Quéva, and Varsha Gandhi. Idelalisib: first-in-class pi3k delta inhibitor for the treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, and follicular lymphoma. Clinical Cancer Research, 21:1537-1542, Mar 2015. URL: https://doi.org/10.1158/1078-0432.ccr-14-2034, doi:10.1158/1078-0432.ccr-14-2034. This article has 268 citations and is from a highest quality peer-reviewed journal.
26. (zhong2013mir30asuppressescell pages 10-10): M. Zhong, Zheng-qian Bian, and Zhiyong Wu. Mir-30a suppresses cell migration and invasion through downregulation of pik3cd in colorectal carcinoma. Cellular Physiology and Biochemistry, 31:209-218, Feb 2013. URL: https://doi.org/10.1159/000343362, doi:10.1159/000343362. This article has 118 citations and is from a peer-reviewed journal.
27. (fruman2017thepi3kpathway pages 2-4): D. Fruman, Honyin Chiu, B. Hopkins, S. Bagrodia, L. Cantley, and R. Abraham. The pi3k pathway in human disease. Cell, 170:605-635, Aug 2017. URL: https://doi.org/10.1016/j.cell.2017.07.029, doi:10.1016/j.cell.2017.07.029. This article has 2643 citations and is from a highest quality peer-reviewed journal.