## Phylogeny

PIK3CD encodes the p110δ catalytic subunit of class IA phosphatidylinositol 3-kinases (PI3Ks), a family of lipid kinases (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, dornan2017conformationaldisruptionof pages 1-2). Unlike typical protein kinases classified by Manning et al., which focuses on the protein kinome, PIK3CD is a lipid kinase belonging to the ‘atypical’ kinase group, reflecting its distinct substrate specificity, structure, and function (fruman2017thepi3kpathway pages 1-2, mcphail2020druggingthephosphoinositide pages 1-3, vanhaesebroeck2016moleculesinmedicine pages 1-3). Within the PI3K family, p110δ is a class IA isoform, phylogenetically related to the other class IA catalytic subunits, p110α (PIK3CA) and p110β (PIK3CB) (dornan2018molecularmechanismsof pages 6-7, nunessantos2019pi3kwaydefects pages 1-2). Orthologs of PIK3CD are conserved across vertebrates, reflecting a conserved role in immune signaling (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, singh2020anupdatedreview pages 12-16).

## Reaction Catalyzed

PIK3CD catalyzes the ATP-dependent phosphorylation of the 3’-hydroxyl group of the inositol ring of phosphoinositides (fruman2017thepi3kpathway pages 1-2, vanhaesebroeck2016moleculesinmedicine pages 1-3). The reaction converts phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) and ATP into the lipid second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3) and ADP (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, berglund2024modulatingthepi3k pages 8-8). The reaction is: ATP + PtdIns(4,5)P2 → ADP + PIP3 (dornan2018molecularmechanismsof pages 6-7).

## Cofactor Requirements

The catalytic activity of p110δ is dependent on divalent metal ions, requiring Mg²⁺ as an essential cofactor for ATP binding and phosphate transfer (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, fruman2017thepi3kpathway pages 1-2, dornan2017conformationaldisruptionof pages 1-2). The requirement for Mg²⁺ is confirmed in in vitro kinase assays (takeda2017novelpik3cdmutations pages 13-16).

## Substrate Specificity

The primary substrate for PIK3CD is the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, dornan2017conformationaldisruptionof pages 1-2). As a lipid kinase, its substrate specificity is distinct from protein kinases; therefore, the consensus substrate motifs identified for serine/threonine and tyrosine kinases in the Johnson et al. and Yaron-Barir et al. papers are not relevant to PIK3CD (dornan2017conformationaldisruptionof pages 1-2, dornan2018molecularmechanismsof pages 6-7, fruman2017thepi3kpathway pages 1-2).

## Structure

The p110δ protein consists of multiple domains: an N-terminal adaptor-binding domain (ABD) for interaction with the p85 regulatory subunit, a Ras-binding domain (RBD), a C2 domain implicated in membrane binding, a helical domain, and a C-terminal kinase domain (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, dornan2017conformationaldisruptionof pages 1-2, fruman2017thepi3kpathway pages 1-2). The kinase domain has a bi-lobal architecture with two key structural features essential for catalysis: the phosphate-binding loop (P-loop) and the catalytic loop (mcphail2020druggingthephosphoinositide pages 1-3, dornan2018molecularmechanismsof pages 1-2). The P-loop interacts with the phosphate groups of ATP, stabilizing the nucleotide in the active site, while the catalytic loop contains residues that facilitate the transfer of the gamma-phosphate from ATP to the lipid substrate (fruman2017thepi3kpathway pages 1-2, mcphail2020druggingthephosphoinositide pages 3-5). A crystal structure of the p110δ/p85α complex (PDB: 5DXU) has provided detailed structural insights (takeda2017novelpik3cdmutations pages 13-16, takeda2017novelpik3cdmutations pages 16-18).

## Regulation

In resting cells, PIK3CD catalytic activity is constitutively inhibited by its association with a p85 regulatory subunit (e.g., PIK3R1) (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2). The p85 subunit maintains inhibition through multiple contacts, including an interface between the p85 nSH2 domain and the p110δ helical domain, as well as contacts involving the p85 iSH2 domain (dornan2017conformationaldisruptionof pages 1-2, dornan2018molecularmechanismsof pages 1-2). Activation is achieved by relieving this inhibition, which occurs when the SH2 domains of p85 bind to phosphotyrosine motifs on activated receptors (e.g., RTKs) or adaptor proteins, recruiting the complex to the membrane (dornan2017conformationaldisruptionof pages 1-2, fruman2017thepi3kpathway pages 2-4). Activity is also allosterically stimulated by the direct binding of active, GTP-bound Ras to the RBD of p110δ (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, nunessantos2019pi3kwaydefects pages 1-2). Post-translational modifications are also involved in modulating its activity (singh2020anupdatedreview pages 12-16).

## Function

PIK3CD is predominantly expressed in hematopoietic cells, particularly B and T lymphocytes, and plays a critical role in immune signaling (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, singh2020anupdatedreview pages 12-16, yang2015idelalisibfirstinclasspi3k pages 16-20). It is activated downstream of various immune receptors, including the B-cell receptor (BCR), T-cell receptor (TCR), Toll-like receptors (TLRs), and co-stimulatory molecules like CD28 (dornan2018molecularmechanismsof pages 1-2, nguyen2021phosphatidylinositol3kinasesignaling pages 1-3, tangye2019immunedysregulationand pages 1-2). The resulting PIP3 production recruits and activates downstream effectors such as AKT and Bruton’s tyrosine kinase (BTK), which in turn regulate crucial cellular functions including proliferation, survival, differentiation, and motility (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, nunessantos2019pi3kwaydefects pages 1-2).

## Inhibitors

Idelalisib is a first-in-class, selective, oral inhibitor of the p110δ isoform (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, yang2015idelalisibfirstinclasspi3k pages 16-20). It has demonstrated clinical efficacy and is approved for the treatment of certain B-cell malignancies, such as chronic lymphocytic leukemia and follicular lymphoma (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, fruman2017thepi3kpathway pages 1-2). Several other potent and selective small-molecule inhibitors targeting p110δ are also in development (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2).

## Other Comments

Germline autosomal dominant gain-of-function mutations in PIK3CD cause a primary immunodeficiency disorder known as Activated PI3K Delta Syndrome (APDS) (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, dornan2018molecularmechanismsof pages 6-7). APDS is characterized by immune dysregulation, recurrent infections, lymphoproliferation, and an increased risk of lymphoma (dornan2017conformationaldisruptionof pages 1-2, tangye2019immunedysregulationand pages 1-2). The most common activating mutation is E1021K in the kinase domain, which is analogous to the oncogenic H1047R mutation in p110α (dornan2018molecularmechanismsof pages 6-7). Other mutations, such as E81K and G124D in the N-terminal region, also cause APDS by disrupting p85-mediated regulation and increasing kinase activity (dornan2018molecularmechanismsof pages 6-7, takeda2017novelpik3cdmutations pages 10-13).

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