## Phylogeny

* Human PIK3C2B encodes phosphatidylinositol-4-phosphate 3-kinase C2-β (PI3K-C2β), one of the three vertebrate class II PI3K catalytic isoforms together with PI3K-C2α and PI3K-C2γ (koch2021themolecularmechanisms pages 1-2).
* Class II PI3Ks constitute a lipid-kinase branch distinct from class I and class III enzymes within the PI3K clade of the kinome (brown2011phylogenomicsofphosphoinositide pages 1-3).
* Mammalian orthologs include mouse Pik3c2b; a single class II ortholog is present in Drosophila melanogaster (Pi3K68D) and Caenorhabditis elegans (piki-1), while budding yeast lacks class II PI3Ks, indicating emergence with multicellularity (margaria2019classiipi3ks pages 9-11, gulluni2019classiipi3k pages 1-2).

## Reaction Catalyzed

ATP + 1-phosphatidyl-1D-myo-inositol → ADP + 1-phosphatidyl-1D-myo-inositol 3-phosphate (PI(3)P) (margaria2019classiipi3ks pages 1-4).  
ATP + 1-phosphatidyl-1D-myo-inositol 4-phosphate → ADP + 1-phosphatidyl-1D-myo-inositol 3,4-bisphosphate (PI(3,4)P₂) (gulluni2019classiipi3k pages 1-2).  
No detectable phosphorylation of phosphatidylinositol-4,5-bisphosphate (PI(4,5)P₂) (margaria2019classiipi3ks pages 1-4).

## Cofactor Requirements

Catalytic activity depends on divalent cations; Mg²⁺ supports activity and its removal reduces kinase output, while class II PI3Ks can also employ Mn²⁺ in vitro (gulluni2019classiipi3k pages 4-5, gulluni2019classiipi3k pages 1-2).

## Substrate Specificity

* Lipid selectivity favours phosphatidylinositol (PI) over PI(4)P as substrate in enzymatic assays (margaria2019classiipi3ks pages 1-4).
* The enzyme does not recognise peptide motifs; consensus sequences are not applicable because catalysis is directed toward membrane phosphoinositides (gulluni2019classiipi3k pages 1-2).

## Structure

* Domain organisation: N-terminal proline-rich segment harbouring a clathrin-binding site and an unverified Ras-binding domain; central C2 domain, helical domain and bilobed kinase core; C-terminal PX domain followed by a second C2 domain (gulluni2019classiipi3k pages 1-2, margaria2019classiipi3ks pages 6-7, unknownauthors2023controlofintegrin pages 35-37).
* The PX-C2 tandem folds onto the kinase domain creating an autoinhibited “clamp” that is released upon binding to PI(4,5)P₂-rich membranes or lysophosphatidic acid (unknownauthors2023controlofintegrin pages 35-37, gulluni2019classiipi3k pages 4-5).
* Catalytic core contains the conserved DFG motif, C-helix and regulatory spine typical of PI3Ks as predicted by AlphaFold model AF-O00750-F1; no high-resolution crystal structure of PI3K-C2β is currently available (koch2021themolecularmechanisms pages 13-14, unknownauthors2022classiiphosphatidylinositol pages 26-29).
* Basic residues in the activation loop constitute a C-terminal “basic box” that enables PI(4)P phosphorylation to PI(3,4)P₂ (unknownauthors2023controlofintegrin pages 35-37).

## Regulation

* N-terminal autoinhibition is relieved by interaction with EGFR and adaptor Grb2 after EGF stimulation (gulluni2019classiipi3k pages 2-4).
* The PX-C2 clamp imposes basal inhibition; engagement of PI(4,5)P₂ or lysophosphatidic acid at membranes unlocks the catalytic core (gulluni2019classiipi3k pages 4-5).
* Thr279 phosphorylation by the mTORC2-dependent kinase PKN2 creates a 14-3-3 docking site that sequesters the kinase in the cytosol under nutrient-rich conditions, whereas dephosphorylation allows Rab7-mediated recruitment to late endosomes/lysosomes during starvation (koch2021themolecularmechanisms pages 9-10).
* TRIM27-driven polyubiquitination negatively regulates PI3K-C2β stability and function in CD4 T cells (gulluni2019classiipi3k pages 21-21).
* Direct clathrin binding targets the enzyme to clathrin-actin structures and enhances catalytic output (wallroth2019phosphoinositideregulationof pages 10-13).
* Interaction with lysosomal Raptor positions the kinase for PI(3,4)P₂ synthesis leading to local mTORC1 inhibition (margaria2019classiipi3ks pages 4-6).

## Function

* Broad tissue expression with particularly high levels in muscle and immune compartments according to transcriptomic surveys (margaria2019classiipi3ks pages 6-7).
* Subcellular localisation encompasses plasma membrane, APPL1⁺ early endosomes, and late endosomes/lysosomes (margaria2019classiipi3ks pages 7-9, koch2021themolecularmechanisms pages 9-10).
* Generates PI(3)P on APPL1⁺ endosomes, driving their maturation to EEA1⁺ compartments and modulating insulin receptor trafficking and AKT activation (margaria2019classiipi3ks pages 7-9).
* Synthesises PI(3,4)P₂ on late endosomes/lysosomes under nutrient deprivation, recruiting 14-3-3 to Raptor and suppressing mTORC1 signalling (koch2021themolecularmechanisms pages 9-10).
* Facilitates clathrin-dependent pinocytosis via its clathrin-binding domain (margaria2019classiipi3ks pages 7-9).
* Promotes lamellipodia and filopodia formation through PI(3)P-dependent activation of CDC42 and RAC, enhancing cell migration (margaria2019classiipi3ks pages 7-9).
* Activates NDPK-B and KCa3.1 channels in T cells and mast cells, supporting Ca²⁺ influx, cytokine production and degranulation (unknownauthors2023controlofintegrin pages 37-40).
* Loss-of-function increases systemic insulin sensitivity and glucose tolerance, indicating antagonism toward PI3K-C2α in insulin signalling (gulluni2019classiipi3k pages 4-5, unknownauthors2023controlofintegrin pages 37-40).

## Inhibitors

* PI3K-C2β is inhibited by the pan-PI3K covalent inhibitor wortmannin but with lower sensitivity than class I isoforms; selective class II inhibitors remain low-potency and scarce (falasca2017classiiphosphoinositide pages 1-2, koch2021themolecularmechanisms pages 13-14).

## Other Comments

* Elevated PIK3C2B expression correlates with increased invasiveness in prostate, breast and ovarian cancers, and depletion diminishes metastatic traits (margaria2019classiipi3ks pages 7-9).
* Muscle-specific Pik3c2b deletion rescues X-linked centronuclear myopathy phenotypes by limiting pathological PI(3)P accumulation (gulluni2019classiipi3k pages 4-5, unknownauthors2023controlofintegrin pages 33-35).
* Copy-number variations of PIK3C2B and related class II genes associate with type 2 diabetes and colorectal cancer outcomes (gulluni2019classiipi3k pages 21-21).
* Global Pik3c2b knockout mice are viable and fertile with no overt developmental phenotype, suggesting redundancy with other PI3Ks (vanhaesebroeck2010theemergingmechanisms pages 1-2).

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