1. Phylogeny  
   PIK3CB is a member of the class I phosphoinositide 3‐kinase family, a group of lipid kinases that is highly conserved throughout eukaryotic evolution (toker2012phosphoinositide3kinases—ahistorical pages 3-6). Within class I, the catalytic subunits are subdivided into class IA and IB isoforms; PIK3CB, which encodes p110β, belongs to the class IA subgroup together with p110α (PIK3CA) and p110δ (PIK3CD) (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). Orthologs of PIK3CB are found in a wide range of vertebrate species, underscoring its fundamental role in receptor‐mediated lipid signaling and cellular homeostasis (OpenTargets Search: -PIK3CB). Comparative analyses indicate that the domain architecture of p110β has been maintained from early eukaryotes to mammals, reflecting the critical nature of its catalytic and regulatory functions in cellular signal transduction (toker2012phosphoinositide3kinases—ahistorical pages 3-6, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5).
2. Reaction Catalyzed  
   PIK3CB catalyzes the phosphorylation of phosphatidylinositol 4,5‐bisphosphate (PIP2) at the 3′‐hydroxyl group of the inositol ring using ATP as a phosphate donor (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2). This reaction generates phosphatidylinositol 3,4,5‐trisphosphate (PIP3) while converting ATP to ADP and releasing a proton, thereby producing a lipid second messenger that is essential for recruiting pleckstrin homology (PH) domain‐containing effector proteins (liu2009targetingthephosphoinositide pages 1-2). The chemical reaction can be summarized as:  
     ATP + PIP2 → ADP + PIP3 + H⁺  
   which is the critical step initiating downstream cellular processes such as cell growth, survival, and motility (akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2, liu2009targetingthephosphoinositide pages 1-2).
3. Cofactor Requirements  
   The kinase activity of PIK3CB depends on the presence of ATP as the phosphate donor, and the reaction requires divalent metal ions for catalytic activity. In particular, Mg²⁺ acts as a necessary cofactor by stabilizing the negative charges on ATP’s phosphate groups during the phosphorylation process (liu2009targetingthephosphoinositide pages 1-2, toker2012phosphoinositide3kinases—ahistorical pages 12-14).
4. Substrate Specificity  
   PIK3CB exhibits high substrate specificity toward phosphatidylinositol derivatives, with a pronounced preference for phosphatidylinositol 4,5‐bisphosphate (PIP2) as its physiological substrate. The enzyme’s catalytic pocket and associated structural elements are optimized to recognize and bind PIP2, allowing for its efficient phosphorylation to produce PIP3, which then functions as a lipid second messenger (liu2009targetingthephosphoinositide pages 18-21, akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2).
5. Structure  
   PIK3CB is a 110 kDa catalytic subunit that exhibits a modular domain organization typical of class I PI3Ks. Its N‐terminal region contains an adaptor‐binding domain (ABD) that mediates tight interactions with p85 regulatory subunits, a feature essential for the stability and regulation of the heterodimeric complex (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). Following the ABD, the protein contains a Ras‐binding domain (RBD) that facilitates interactions with small GTPases such as Ras, thereby linking extracellular receptor signals to its activation (akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). Immediately downstream, a C2 domain is present; this domain contributes predominantly to membrane association by binding phospholipids in a calcium‐independent manner. Adjacent to the C2 domain, a helical domain is found, which plays a role in the regulation of catalytic activity and may help mediate conformational changes upon activation (toker2012phosphoinositide3kinases—ahistorical pages 12-14). The C‐terminal portion of PIK3CB is dominated by the kinase catalytic domain, which adopts a bilobal structure in accordance with the general architecture of protein kinases; the smaller N‐lobe primarily binds ATP while the larger C‐lobe forms the binding site for the lipid substrate (liu2009targetingthephosphoinositide pages 4-5, toker2012phosphoinositide3kinases—ahistorical pages 10-12). Within this kinase domain lie several critical motifs, including the activation loop, a hydrophobic spine, and the C‐helix, all of which are essential for catalytic function and proper conformational dynamics. Structural studies have revealed that this domain organization not only ensures efficient kinase activity but also allows for precise regulation by the p85 subunit and by interactions with small GTPases, thereby integrating signals from both receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) (toker2012phosphoinositide3kinases—ahistorical pages 8-10, liu2009targetingthephosphoinositide pages 7-8). The overall three-dimensional organization supports a mechanism in which membrane interaction, mediated in part by the C2 domain, positions the kinase domain in close proximity to its lipid substrate, facilitating the localized production of PIP3 at specific membrane microdomains (toker2012phosphoinositide3kinases—ahistorical pages 10-12).
6. Regulation  
   The regulation of PIK3CB is achieved through a confluence of protein–protein interactions and allosteric mechanisms that modulate its catalytic activity. Under basal conditions, PIK3CB forms a heterodimer with p85 regulatory subunits; these subunits engage in inhibitory interactions via their nSH2 and cSH2 domains, which maintain the catalytic subunit in an inactive conformation by obstructing access to the active site (toker2012phosphoinositide3kinases—ahistorical pages 3-6, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). Upon activation by extracellular cues, such as ligand binding to receptor tyrosine kinases, phosphorylated tyrosine residues on receptors or adaptor proteins are recognized by the SH2 domains of p85, leading to a displacement of the inhibitory contacts and subsequent recruitment of the PI3K complex to the plasma membrane (toker2012phosphoinositide3kinases—ahistorical pages 8-10). In addition to RTK-mediated activation, PIK3CB is also activated downstream of G-protein coupled receptor (GPCR) signaling; here, direct interactions with Gβγ subunits serve to further facilitate a conformational change that alleviates autoinhibition and increases catalytic activity (liu2009targetingthephosphoinositide pages 7-8, toker2012phosphoinositide3kinases—ahistorical pages 16-16). The Ras-binding domain contributes an additional layer of regulation by engaging with GTP-bound Ras, thereby linking signals from both RTKs and GPCRs to the activation of PIK3CB. Although specific post-translational modifications such as phosphorylation events have been implicated in modulating PI3K activity in general, the current context does not provide detailed modification sites for PIK3CB; however, such modifications are known to impact the interaction between the catalytic and regulatory subunits in related isoforms (dirican2017phosphatidylinositol3kinaseregulatory pages 10-11). Through this multifactorial regulation, PIK3CB is able to integrate a variety of extracellular signals and mediate a timely and spatially restricted production of its lipid product, ensuring precise control of downstream signaling pathways.
7. Function  
   PIK3CB plays a central role in signal transduction by converting PIP2 to PIP3, thereby generating a lipid second messenger that is critical for the activation of downstream effector proteins equipped with pleckstrin homology (PH) domains. The local accumulation of PIP3 at the plasma membrane facilitates the recruitment of key signaling molecules such as AKT and 3-phosphoinositide-dependent protein kinase-1 (PDPK1), thus initiating cascades that regulate cell growth, survival, proliferation, motility, and morphological changes (OpenTargets Search: -PIK3CB, akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2). PIK3CB is activated in response to ligands that engage GPCRs – including agents like CXCL12, sphingosine 1-phosphate, and lysophosphatidic acid – as well as via receptor tyrosine kinases, thereby positioning it at a confluence of multiple signaling pathways (liu2009targetingthephosphoinositide pages 1-2, akinleye2013phosphatidylinositol3kinase(pi3k) pages 1-2). In addition to its well-established role in growth and survival signaling, PIK3CB is critical for platelet function; it participates in stable platelet adhesion and aggregation by transducing signals from GPCRs, integrins such as αIIbβ3, and immunoreceptor tyrosine-based activation motifs (ITAMs) (liu2009targetingthephosphoinositide pages 7-8, akinleye2013phosphatidylinositol3kinase(pi3k) pages 2-5). As a consequence, PIK3CB contributes to the regulation of hemostasis as well as to the broader control of cellular processes that are essential for maintaining tissue homeostasis.
8. Other Comments  
   Selective inhibition of PIK3CB is of considerable therapeutic interest given its involvement in diverse pathological conditions. Although direct mutations in PIK3CB are less frequent compared to those observed in PIK3CA, aberrant expression or dysregulated activation of p110β has been implicated in oncogenic processes and may play a particularly prominent role in certain PTEN-deficient tumors (liu2009targetingthephosphoinositide pages 7-8, toker2012phosphoinositide3kinases—ahistorical pages 8-10). Isoform-selective inhibitors such as TGX-221 have been developed for experimental studies and are under investigation for their potential to modulate disease states characterized by hyperactive PI3K signaling. In addition to its role in cancer, the contribution of PIK3CB to platelet activation has raised interest in its potential as a target for anti-thrombotic therapies. Its dual activation by receptor tyrosine kinases and GPCRs underscores its versatility as a signaling node; consequently, efforts to develop inhibitors that effectively target PIK3CB must take into account the enzyme’s complex regulatory interactions and its integration within multiple signaling networks (OpenTargets Search: -PIK3CB, liu2009targetingthephosphoinositide pages 18-21).
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