1. Phylogeny  
   Phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3), commonly referred to as VPS34 or hVps34, represents the sole member of the class III phosphoinositide 3‑kinases and is highly conserved from yeast to mammals, indicating an ancestral origin that dates back to the Last Eukaryotic Common Ancestor (LECA) (philippon2015evolutionaryhistoryof pages 1-2). VPS34 is ubiquitously present across eukaryotic lineages including fungi, plants, and metazoans, and its evolutionary conservation distinguishes it from class I and II PI3Ks that are typically restricted to Unikonta and subsequently diverged under different selective pressures (philippon2015evolutionaryhistoryof pages 2-4, okkenhaug2013signalingbythe pages 1-3). Phylogenetically, VPS34 clusters into a monophyletic group within the PI3K kinome, and its existence as a single catalytic subunit reinforces its indispensable role in lipid signaling and vesicle trafficking in all eukaryotes (burke2018structuralbasisfor pages 2-2). The close evolutionary relationship of VPS34 with its regulatory partner VPS15, which assists in enzyme stabilization and membrane recruitment, further confirms that the class III PI3K complex constitutes an evolutionarily ancient and functionally distinct signaling module relative to other PI3K classes (philippon2015evolutionaryhistoryof pages 14-15, okkenhaug2013signalingbythe pages 1-3).
2. Reaction Catalyzed  
   PIK3C3 catalyzes the transfer of a phosphate group from ATP to phosphatidylinositol (PI), resulting in the formation of phosphatidylinositol 3‑phosphate (PI3P), ADP, and a proton, thereby establishing the fundamental biochemical reaction that underpins its role in lipid signaling (burke2018structuralbasisfor pages 2-2). This reaction can be summarized as: ATP + PI → ADP + PI3P + H⁺, and it is critical for the subsequent recruitment of PI3P‐binding proteins that regulate membrane trafficking events and autophagosome formation (craene2017phosphoinositidesmajoractors pages 9-11).
3. Cofactor Requirements  
   The enzymatic activity of PIK3C3 is dependent on the presence of ATP as the phosphate donor, and like many kinases, its catalytic mechanism requires a divalent metal ion cofactor, typically Mg²⁺, to facilitate proper substrate binding and phosphoryl transfer (burke2018structuralbasisfor pages 20-21, li2024targetingpi3kfamily pages 2-5). The requirement of Mg²⁺ is fundamental to stabilize the negative charge of ATP and aid in the formation of the enzyme–substrate complex, ensuring efficient catalysis on membrane-associated phosphatidylinositol substrates (ohashi2021activationmechanismsof pages 1-2).
4. Substrate Specificity  
   PIK3C3 exhibits a high degree of substrate specificity by exclusively phosphorylating phosphatidylinositol (PI) at the D3 position of the inositol ring, thereby generating PI3P, which serves as a key lipid signaling molecule at intracellular membranes (craene2017phosphoinositidesmajoractors pages 15-17, burke2018structuralbasisfor pages 2-2). The enzyme’s catalytic domain is structured to engage the inositol headgroup of PI and to orient it optimally for phosphorylation, and this strict substrate specificity distinguishes it from class I PI3Ks, which use phosphatidylinositol 4,5‑bisphosphate as a substrate (ohashi2021activationmechanismsof pages 18-19). Additionally, the activity of VPS34 is modulated by membrane lipid composition, where factors such as unsaturation and membrane curvature can influence substrate presentation, thereby enhancing the production of PI3P in specific cellular contexts like autophagosome initiation (li2024targetingpi3kfamily pages 8-10).
5. Structure  
   PIK3C3 is organized as a multidomain protein that includes an N‑terminal C2 domain, a central helical domain, and a C‑terminal catalytic kinase domain, each of which plays a distinct role in the enzyme’s function and regulation (burke2018structuralbasisfor pages 4-5, nakadatsukui2019phosphatidylinositolkinasesand pages 13-14). The C2 domain, although named for its resemblance to Ca²⁺‑binding modules, in VPS34 functions more as a structural scaffold that facilitates protein–protein interactions rather than mediating membrane binding directly (burke2018structuralbasisfor pages 8-10). The helical domain contributes to the structural integrity of the enzyme and is implicated in mediating contacts with regulatory subunits within the PI3K complex (li2024targetingpi3kfamily pages 5-7). The kinase domain of VPS34 is arranged into a typical bilobal structure comprising an N‑lobe and a larger C‑lobe, with the nucleotide binding pocket located at the interface, and features conserved motifs such as the P‑loop, the activation loop, and a catalytic loop containing DFG and DHR motifs that are essential for activity (ohashi2021activationmechanismsof pages 4-6, burke2018structuralbasisfor pages 5-6). Structural studies have revealed that VPS34 assembles with regulatory proteins such as VPS15 and Beclin 1 into discrete multiprotein complexes that adopt a characteristic V‑shaped architecture; in complex I, association with ATG14L and NRBF2 facilitates autophagosome initiation, whereas in complex II, complex assembly with UVRAG directs the enzyme toward roles in endocytic trafficking and autophagosome maturation (burke2018structuralbasisfor pages 10-11, li2024targetingpi3kfamily pages 5-7, nakadatsukui2019phosphatidylinositolkinasesand pages 8-10). Unique structural features include the ability of VPS34 to undergo conformational rearrangements upon membrane binding, which relieve autoinhibitory contacts imposed by VPS15 and promote catalysis (ohashi2021activationmechanismsof pages 7-9).
6. Regulation  
   Regulation of PIK3C3 is achieved primarily through its assembly into distinct multiprotein complexes and through post‑translational modifications that modulate its catalytic efficiency and subcellular localization (burke2018structuralbasisfor pages 11-12, ohashi2021activationmechanismsof pages 10-12). In complex I, which includes regulatory components such as Beclin 1, ATG14L, and NRBF2, the association with these proteins dictates its activation during autophagy initiation, while in complex II the exchange of ATG14L for UVRAG and the presence of Rubicon impinge on endocytic trafficking and autophagosome maturation (li2024targetingpi3kfamily pages 5-7, craene2017phosphoinositidesmajoractors pages 13-15). Specific phosphorylation events are known to regulate VPS34 activity; for example, phosphorylation by AMPK and mTOR has been reported to inhibit or alter the activity of certain VPS34 complexes in a context‑dependent manner, and acetylation at key lysine residues may affect substrate binding and complex formation (burke2018structuralbasisfor pages 16-16, ohashi2021activationmechanismsof pages 22-24). Additionally, interactions with small GTPases such as Rab5 and Rab1 further promote membrane recruitment and relieve autoinhibition via binding to the C2 helical hairpin in the C2 domain, thereby coordinating VPS34 activity with vesicular trafficking processes (ohashi2021activationmechanismsof pages 4-6, okkenhaug2013signalingbythe pages 4-6). The overall regulatory mechanism is thus multifactorial, involving both reversible post‑translational modifications and dynamic association with accessory proteins that define the subcellular functions of PIK3C3 in autophagy and endocytosis (burke2018structuralbasisfor pages 17-18, nakadatsukui2019phosphatidylinositolkinasesand pages 6-8).
7. Function  
   PIK3C3 serves as the catalytic engine of the class III PI3K complexes, mediating the synthesis of PI3P from PI, which is critical for the formation and maturation of membrane compartments involved in vesicle trafficking and autophagy (craene2017phosphoinositidesmajoractors pages 15-17, burke2018structuralbasisfor pages 19-20). In the context of autophagy, the PI3KC3-C1 complex, which includes VPS34 together with VPS15, Beclin 1, ATG14L, and NRBF2, facilitates the initiation of autophagosomes by promoting endoplasmic reticulum membrane curvature and vesicle budding (li2024targetingpi3kfamily pages 8-10, ohashi2021activationmechanismsof pages 15-17). Conversely, the PI3KC3-C2 complex, defined by the replacement of ATG14L with UVRAG, plays a pivotal role in the maturation of autophagosomes, degradative endocytic trafficking, and the abscission step in cytokinesis, and it is required for the transport of lysosomal enzyme precursors to lysosomes as well as for the transition from early to late endosomes (craene2017phosphoinositidesmajoractors pages 9-11, li2024targetingpi3kfamily pages 41-42). Furthermore, PIK3C3-generated PI3P serves as a docking site for effector proteins containing FYVE and PX domains, which are essential for recruiting additional proteins that coordinate membrane fusion, fission, and vesicular sorting events necessary for cellular homeostasis (burke2018structuralbasisfor pages 2-4, ohashi2021activationmechanismsof pages 33-34). In immune cells, PI3P production by VPS34 contributes to the maturation of phagosomes as well as the regulation of autophagic responses that are critical in pathogen clearance, and the enzyme is implicated in the regulation of intracellular signaling pathways linked to endocytic recycling and nutrient sensing (okkenhaug2013signalingbythe pages 4-6, philippon2015evolutionaryhistoryof pages 15-15).
8. Other Comments  
   Several potent and selective inhibitors targeting PIK3C3 have been developed, including SAR405, VPS34‑IN1, and PIK‑III, which have demonstrated low nanomolar inhibitory activity and have been employed as chemical probes to modulate autophagy and vesicular trafficking in preclinical studies (li2024targetingpi3kfamily pages 29-31, li2024targetingpi3kfamily pages 42-42). Dysregulation of VPS34 has been associated with diverse pathological conditions such as cancer, neurodegenerative disorders, and metabolic diseases, largely due to its central role in controlling autophagic flux and endocytic sorting (craene2017phosphoinositidesmajoractors pages 15-17, ohashi2021activationmechanismsof pages 19-21). Although direct disease‑associated mutations in PIK3C3 are not as frequently reported as those in class I PI3Ks, alterations in the regulatory subunits of the VPS34 complexes have been implicated in defective autophagy, impaired cytokinesis, and disruptions in endosomal maturation (burke2018structuralbasisfor pages 17-18, li2024targetingpi3kfamily pages 8-10). Ongoing efforts to further characterize the molecular details of VPS34 regulation and its interactions with various accessory proteins continue to provide a framework for the rational design of therapeutic agents to specifically target aberrant PI3K signaling in diseases (ohashi2021activationmechanismsof pages 25-26, okkenhaug2013signalingbythe pages 16-17).
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