1. Phylogeny  
   PIK3CA encodes the p110α catalytic subunit of class IA phosphoinositide 3‐kinases, a group of enzymes that are evolutionarily well conserved among metazoans. Orthologs of PIK3CA can be detected across a wide range of eukaryotic species, with its emergence coinciding with the appearance of complex receptor‐mediated signaling pathways. In evolutionary analyses, class IA catalytic subunits – including p110α – cluster together and are shown to have arisen from a gene duplication event that occurred in the common ancestor of animals and fungi. Moreover, within the broader kinome, PIK3CA is part of a conserved signaling core that also encompasses key regulatory proteins such as PTEN, mTOR, AKT, and several other kinases instrumental to growth factor signaling and cellular homeostasis. This conservation underscores the enzyme’s fundamental role in diverse cellular processes and highlights its integration into the evolutionary network of signaling cascades that trace back to the Last Eukaryotic Common Ancestor (philippon2015evolutionaryhistoryof pages 1-2, scheeff2005structuralevolutionof pages 1-2, okkenhaug2013signalingbythe pages 28-32).
2. Reaction Catalyzed  
   PIK3CA catalyzes the phosphorylation reaction in which ATP donates a phosphate group to phosphatidylinositol 4,5‐bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5‐trisphosphate (PIP3). In biochemical terms, the reaction can be summarized as follows:  
     ATP + PIP2 → ADP + PIP3 + H⁺  
   This reaction is fundamental to the generation of a lipid second messenger, PIP3, which is essential for the recruitment and activation of downstream effector proteins that contain pleckstrin homology (PH) domains (bissegger2024rapidpotentand pages 14-15).
3. Cofactor Requirements  
   The catalytic activity of PIK3CA is dependent on the presence of ATP as the phosphate donor. In addition, as is characteristic of many kinases, the enzyme’s activity requires divalent metal cations—most commonly Mg²⁺—which are necessary for coordinating the ATP molecule within the active site and facilitating the phosphotransfer reaction (bissegger2024rapidpotentand pages 14-15, okkenhaug2013signalingbythe pages 6-8).
4. Substrate Specificity  
   PIK3CA exhibits stringent substrate specificity for phosphatidylinositol 4,5‐bisphosphate. The enzyme recognizes the inositol head group of PIP2 and precisely orients the 3′ hydroxyl group for phosphate transfer. This specificity is achieved through conserved structural elements within the catalytic domain that form a binding pocket complementary to the spatial arrangement of the phosphate groups on PIP2. Because the formation of PIP3 is essential for the recruitment of PH domain–containing proteins, the substrate specificity of PIK3CA represents a critical checkpoint in the propagation of downstream signaling cascades. The selectivity for PIP2 over other phosphoinositide substrates underpins its pivotal function in modulating signaling responses to growth factor stimulation (bissegger2024rapidpotentand pages 14-15, czyzyk2025structuralinsightsinto pages 1-2, okkenhaug2013signalingbythe pages 6-8).
5. Structure  
   PIK3CA’s three-dimensional structure is organized into several domains, each with distinct functions that contribute to its overall catalytic activity and regulation. At the N-terminus lies the adaptor-binding domain (ABD), which is responsible for binding the regulatory subunit p85. This interaction not only stabilizes the catalytic subunit but also serves as an important mechanism of autoinhibition under basal conditions. Adjacent to the ABD is the Ras-binding domain (RBD), which mediates interactions with activated Ras family GTPases. Binding of Ras to the RBD facilitates the translocation of PIK3CA to the plasma membrane, where its substrate PIP2 is abundant.

Following these domains, the enzyme contains a C2 domain that contributes to membrane association by binding to phospholipids, thereby positioning the catalytic module in close proximity to its lipid substrates. Immediately downstream is the helical domain, which plays a critical role in modulating the conformation of the catalytic domain. This domain is also recognized as a hotspot for oncogenic mutations that relieve autoinhibition and lead to enhanced kinase activity. Finally, the C-terminal catalytic kinase domain carries out the phosphoryl transfer reaction. Within the kinase domain, key structural features include an activation loop that undergoes conformational changes upon activation, the positioning of the C-helix critical for ATP binding, and a hydrophobic spine that contributes to the stability of the active conformation. Crystal structures and co-crystallization studies have confirmed the spatial arrangement of these domains and highlighted how domain interactions and conformational rearrangements underpin the activation and regulation of PIK3CA (czyzyk2025structuralinsightsinto pages 1-2, czyzyk2025structuralinsightsinto pages 13-15, bissegger2024rapidpotentand pages 10-12).

1. Regulation  
   The regulation of PIK3CA is multifaceted and involves numerous mechanisms that ensure its activity is tightly controlled in response to extracellular cues. In the basal state, PIK3CA forms a heterodimer with the regulatory p85 subunit. This p85 subunit binds to the adaptor-binding domain at the N-terminus of PIK3CA, maintaining the enzyme in an autoinhibited conformation. Upon stimulation by growth factors such as EGF, insulin, IGF1, VEGFA, and PDGF, receptor tyrosine kinases become activated and phosphorylate specific tyrosine residues on their intracellular domains. These phosphorylated motifs serve as docking sites for the SH2 domains of p85, resulting in the recruitment of the PI3K heterodimer to the plasma membrane and alleviation of autoinhibition.

Furthermore, PIK3CA is regulated by its interaction with Ras. The binding of GTP-loaded Ras to the Ras-binding domain enhances membrane recruitment and increases catalytic efficiency by promoting a conformational shift that favors activation. In addition, feedback loops from downstream signaling pathways, including those involving AKT and mTOR, can modulate PIK3CA activity by affecting its phosphorylation status and stability. Although specific phosphorylation sites on PIK3CA are less well characterized in comparison to other kinases, these post-translational modifications, along with regulatory interactions with adaptor proteins and allosteric effectors, provide critical control over its activity. Collectively, these regulatory mechanisms ensure that PIK3CA activity is transiently elevated in response to appropriate signals and rapidly attenuated to prevent aberrant cellular proliferation (bissegger2024rapidpotentand pages 14-15, czyzyk2025structuralinsightsinto pages 13-15, okkenhaug2013signalingbythe pages 4-6).

1. Function  
   PIK3CA is central to many aspects of cellular signaling due to its role in generating PIP3, a lipid second messenger that is pivotal for the activation of downstream signaling pathways. By phosphorylating PIP2 to produce PIP3, PIK3CA enables the recruitment of PH domain–containing proteins such as AKT1 and PDPK1 to the plasma membrane. This recruitment is the initiating step of the PI3K/AKT/mTOR pathway, which governs a broad range of cellular processes including cell survival, growth, proliferation, motility, and metabolism.

In response to extracellular stimuli, activation of PIK3CA leads to increased PIP3 levels and subsequent AKT activation, which in turn phosphorylates numerous substrates involved in promoting cell cycle progression and inhibiting apoptosis. In endothelial cells, PIK3CA has an essential role in mediating VEGFA-induced cell migration, a process critical for angiogenesis and vascular development. The downstream effects of PIK3CA signaling also extend to metabolic reprogramming and cytoskeletal rearrangements, thereby influencing cell morphology and motility. Given that activating mutations in PIK3CA are among the most common genetic alterations in cancers such as breast, colorectal, thyroid, and ovarian carcinomas, the normal regulatory and functional roles of PIK3CA are underscored by its contribution to oncogenic signaling when aberrantly activated (bissegger2024rapidpotentand pages 14-15, czyzyk2025structuralinsightsinto pages 1-2, okkenhaug2013signalingbythe pages 20-21, rinne2021targetingthepi3kaktmtor pages 20-21).

1. Other Comments  
   Owing to its pivotal role in controlling diverse cellular functions via the production of PIP3, PIK3CA is frequently subject to oncogenic mutations that lead to its constitutive activation. Activating mutations, typically located in the helical and kinase domains, are known to disrupt autoinhibitory interactions and promote persistent downstream signaling through the AKT/mTOR pathway. In the context of cancer therapy, PIK3CA has emerged as an important therapeutic target; selective inhibitors such as alpelisib (BYL719) have been approved for clinical use in cancers harboring PIK3CA mutations. In addition, recent studies have described the development of covalent inhibitors that irreversibly bind to a conserved cysteine residue within the ATP-binding pocket, offering the potential for enhanced potency and sustained inhibition. These chemical probes are also valuable experimental tools for dissecting isoform-specific signaling networks mediated by PI3Kα. The aberrant activation of PIK3CA not only drives oncogenesis but also contributes to resistance mechanisms against conventional therapies, thereby reinforcing its significance as both a biomarker and drug target in precision oncology (bissegger2024rapidpotentand pages 14-15, bissegger2024rapidpotentand pages 18-18, czyzyk2025structuralinsightsinto pages 13-15, okkenhaug2013signalingbythe pages 6-8, philippon2015evolutionaryhistoryof pages 14-15).
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