## Phylogeny

The PIK3CA gene encodes the p110α catalytic subunit, which is a Class IA phosphoinositide 3-kinase (PI3K) (burke2018structuralbasisfor pages 5-6, brown2011phylogenomicsofphosphoinositide pages 1-3). The PI3K family is classified within the Atypical kinase group in the human kinome, distinct from the AGC kinase family (leontiadou2018insightsintothe pages 14-14, brown2011phylogenomicsofphosphoinositide pages 8-9). The protein is evolutionarily conserved, with orthologs identified across vertebrates and deuterostome lineages, including the sea urchin (*Strongylocentrotus purpuratus*), tunicate (*Ciona intestinalis*), and cephalochordate (*Branchiostoma floridae*) (brown2011phylogenomicsofphosphoinositide pages 8-9, burke2018structuralbasisfor pages 5-6).

## Reaction Catalyzed

The enzyme catalyzes the ATP-dependent phosphorylation of the 3-position of the inositol ring of phosphatidylinositols (burke2012oncogenicmutationsmimic pages 1-1, huang2008insightsintothe pages 5-7). Specifically, it converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), generating ADP as a product (huang2008insightsintothe pages 1-2, zhao2008classipi3k pages 1-2).

## Cofactor Requirements

The catalytic activity of p110α requires Mg²⁺ as a cofactor for phosphoryl transfer (brown2011phylogenomicsofphosphoinositide pages 1-3, wang2017theimpactof pages 7-11).

## Substrate Specificity

PIK3CA functions primarily as a lipid kinase with specificity for phosphatidylinositol lipids such as PIP2 (huang2008insightsintothe pages 4-5, leontiadou2018insightsintothe pages 14-14, vogt2023structuralandmechanistic pages 4-6). It also exhibits protein kinase activity, capable of phosphorylating its associated regulatory subunit, p85α, on Ser608 (unknownauthors2006regulationofclass pages 35-37). There is less evidence for defined consensus motifs for other protein substrates (wang2017theimpactof pages 20-26, vogt2023structuralandmechanistic pages 4-6).

## Structure

The p110α catalytic subunit is composed of five domains: an N-terminal adaptor-binding domain (ABD) that interacts with the p85 regulatory subunit, a Ras-binding domain (RBD), a C2 domain involved in membrane binding, a helical domain that participates in regulatory interactions, and a C-terminal kinase domain that performs catalysis (burke2012oncogenicmutationsmimic pages 1-1, vogt2007cancerspecificmutationsin pages 3-5, zhao2008classipi3k pages 2-4). Crystal structures of the human p110α/p85α complex have been resolved (e.g., PDB IDs 2RD0, 4OVU) (gkeka2014investigatingthestructure pages 11-12, leontiadou2018insightsintothe pages 12-14). Key structural features within the kinase domain include the ATP-binding site, a conserved C-helix, a P-loop, a catalytic loop, and an activation loop, which are critical for enzymatic function and regulation (brown2011phylogenomicsofphosphoinositide pages 1-3, gkeka2014investigatingthestructure pages 11-12).

## Regulation

The activity of p110α is regulated by allosteric mechanisms and post-translational modifications (PTMs). In its basal state, p110α is inhibited by the p85 regulatory subunit (burke2012oncogenicmutationsmimic pages 1-1). Activation occurs when the SH2 domains of p85 bind to phosphotyrosine motifs on receptor tyrosine kinases (RTKs), relieving inhibitory contacts, or through the direct binding of GTP-bound Ras to the p110α RBD (burke2012oncogenicmutationsmimic pages 1-1, liu2014thestructuralbasis pages 1-2, zhao2008classipi3k pages 2-4). PTMs provide further layers of control. The protein kinase activity of p110α phosphorylates its p85α regulatory subunit on Ser608, which reduces PI3K lipid kinase activity by approximately 80% (unknownauthors2006regulationofclass pages 35-37). Protein kinase C alpha (PKCα) phosphorylates p110α on serine residues, which also partially inhibits its lipid kinase activity (unknownauthors2006regulationofclass pages 35-37). Additionally, p110α is tyrosine phosphorylated by kinases such as Lck, which modulates its association with receptor complexes (unknownauthors2006regulationofclass pages 35-37). Ubiquitination exerts dual control over p110α: the E3 ligase NEDD4L targets it for proteasomal degradation, reducing its stability, whereas the E3 ligase TRAF6 ubiquitinates p110α to enhance its kinase activity and downstream signaling (wang2018traf6interactswith pages 21-26, wang2018traf6interactswith pages 14-18).

## Function

PIK3CA is widely expressed across many tissues (wang2017theimpactof pages 1-7, wang2017theimpactof pages 7-11). It is a crucial enzyme in the PI3K/AKT/mTOR signaling pathway, which regulates fundamental cellular processes including cell growth, proliferation, survival, and metabolism (huang2008insightsintothe pages 1-2, zhao2008classipi3k pages 1-2). Upstream signals from RTKs and G-protein coupled receptors (GPCRs) activate PI3K (zhao2008classipi3k pages 2-4). The resulting production of the second messenger PIP3 recruits downstream effectors containing Pleckstrin homology (PH) domains, such as the kinases AKT and PDK1, to the plasma membrane (huang2008insightsintothe pages 1-2). This leads to the activation of AKT, which then phosphorylates a wide array of substrates including TSC, FOXO1, GSK3β, and effectors of mTOR like S6K and 4E-BP1 (zhao2008classipi3k pages 2-4, vogt2007cancerspecificmutationsin pages 3-5). The tumor suppressor PTEN acts as a negative regulator of this pathway by dephosphorylating PIP3 (flanagan2014structurefunctionand pages 1-2, huang2008insightsintothe pages 1-2).

## Inhibitors

Both pan-PI3K and isoform-selective inhibitors have been developed. Broad-spectrum inhibitors include wortmannin and LY294002 (huang2008insightsintothe pages 5-7). Isoform-specific inhibitors targeting p110α include Alpelisib (BYL-719) and Inavolisib (GDC-0077) (burke2018structuralbasisfor pages 2-4, vogt2023structuralandmechanistic pages 7-8). Other compounds targeting the pathway include NVP-BEZ235 and SF-1126, as well as inhibitors of the downstream kinase AKT, such as API-2 and GSK690693 (wang2017theimpactof pages 38-39, wang2017theimpactof pages 20-26).

## Other Comments

PIK3CA is one of the most frequently mutated genes in human cancers, including breast, colorectal, endometrial, and gastric carcinomas (burke2012oncogenicmutationsmimic pages 1-1, chalhoub2009ptenandthe pages 5-7). Approximately 80% of these oncogenic mutations are gain-of-function and cluster at three hotspots: E542K and E545K in the helical domain, and H1047R in the kinase domain (chalhoub2009ptenandthe pages 5-7, zhao2008classipi3k pages 1-2). Helical domain mutations cause constitutive activation by disrupting inhibitory contacts with the nSH2 domain of the p85 regulatory subunit, thereby mimicking RTK-mediated activation (burke2012oncogenicmutationsmimic pages 1-1, wang2017theimpactof pages 11-16). The H1047R kinase domain mutation enhances catalytic activity by altering the conformation of the activation loop and increasing the enzyme’s affinity for the cell membrane (burke2012oncogenicmutationsmimic pages 1-1, huang2008insightsintothe pages 4-5). Other less common oncogenic mutations in the ABD (e.g., R88A) and C2 domain (e.g., N345K) also enhance kinase activity by relieving inhibitory interactions or increasing membrane affinity (zhao2008classipi3k pages 4-5).

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