## Phylogeny

The human PIK3CA gene encodes the Class IA phosphoinositide-3-kinase catalytic subunit p110α, positioned within the atypical protein kinase group and phylogenetically distinct from the AGC family (Brown & Auger, 2011; Burke, 2018). Orthologues are conserved throughout vertebrates and other deuterostomes, including sea urchin (Strongylocentrotus purpuratus), tunicate (Ciona intestinalis) and amphioxus (Branchiostoma floridae) (Brown & Auger, 2011; Burke, 2018).

## Reaction Catalyzed

ATP + phosphatidylinositol-4,5-bisphosphate ⇌ ADP + phosphatidylinositol-3,4,5-trisphosphate (Huang et al., 2008; Zhao & Vogt, 2008).

## Cofactor Requirements

Mg²⁺ is required for phosphoryl-transfer activity (Brown & Auger, 2011; Wang et al., 2017).

## Substrate Specificity

p110α functions primarily as a lipid kinase preferring PIP2 as substrate (Huang et al., 2008; Leontiadou et al., 2018; Vogt et al., 2023). It also displays protein kinase activity, autophosphorylating the regulatory subunit p85α on Ser608; additional protein targets and consensus motifs are poorly defined (Unknown authors, 2006; Wang et al., 2017).

## Structure

The catalytic subunit comprises an N-terminal adaptor-binding domain (ABD), Ras-binding domain (RBD), C2 membrane-binding domain, helical domain, and C-terminal kinase domain (Burke et al., 2012; Vogt et al., 2007; Zhao & Vogt, 2008). Crystal structures of the human p110α/p85α complex (e.g., PDB 2RD0, 4OVU) reveal canonical kinase motifs: ATP-binding pocket, C-helix, P-loop, catalytic loop and activation loop (Gkeka et al., 2014; Vogt et al., 2023).

## Regulation

Basally inhibited by p85; activation follows SH2-mediated engagement of phosphotyrosine motifs on receptor tyrosine kinases or binding of GTP-Ras to the RBD (Burke et al., 2012; Liu et al., 2014). Post-translational control includes:  
• Autophosphorylation of p85α Ser608, reducing lipid-kinase activity (~80 %) (Unknown authors, 2006).  
• PKCα-mediated serine phosphorylation of p110α, partially inhibitory (Unknown authors, 2006).  
• Tyrosine phosphorylation by Lck, modulating receptor association (Unknown authors, 2006).  
• Ubiquitination: NEDD4L promotes proteasomal degradation, whereas TRAF6 ubiquitination enhances catalytic activity (Wang et al., 2018).

## Function

PIK3CA is broadly expressed in human tissues (Wang et al., 2017). Within the PI3K/AKT/mTOR pathway, p110α converts PIP2 to PIP3, recruiting PH-domain effectors such as AKT and PDK1 to the plasma membrane (Huang et al., 2008). Activated AKT phosphorylates substrates including TSC, FOXO1, GSK3β and mTOR effectors S6K and 4E-BP1, promoting cell growth, survival and metabolism (Zhao & Vogt, 2008; Vogt et al., 2007). PTEN opposes this signal by dephosphorylating PIP3 (Flanagan & Shepherd, 2014; Chalhoub & Baker, 2009).

## Inhibitors

Pan-PI3K inhibitors: wortmannin, LY294002 (Huang et al., 2008).  
p110α-selective inhibitors: Alpelisib (BYL-719), Inavolisib (GDC-0077) (Burke, 2018; Vogt et al., 2023).  
Pathway-targeting agents: NVP-BEZ235, SF-1126, and downstream AKT inhibitors API-2, GSK690693 (Wang et al., 2017).

## Other Comments

PIK3CA ranks among the most frequently mutated oncogenes in breast, colorectal, endometrial and gastric cancers (Burke et al., 2012; Chalhoub & Baker, 2009). Roughly 80 % of activating mutations cluster at E542K and E545K (helical domain) or H1047R (kinase domain). Helical mutations disrupt inhibitory nSH2 interactions, mimicking receptor activation; H1047R promotes an open activation loop and enhanced membrane affinity (Burke et al., 2012; Huang et al., 2008). Additional gain-of-function variants in the ABD (R88A) and C2 (N345K) domains also relieve autoinhibition or improve membrane engagement (Zhao & Vogt, 2008).

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