## Phylogeny

PIK3CB (p110β) is a Class IA phosphoinositide-3-kinase catalytic subunit that clusters with the other Class I isoforms PIK3CA (p110α) and PIK3CG (p110γ) (Brown & Auger, 2011). Well-conserved orthologues occur throughout vertebrates (Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Tetraodon nigroviridis) and more distantly in Deuterostomia, Tunicata and Cephalochordata, indicating broad conservation across chordates (Brown & Auger, 2011). PI3Ks are placed outside conventional eukaryotic protein-kinase groups and are sometimes referred to as “atypical” kinases (Nakanishi et al., 2016; Burke, 2018).

## Reaction Catalyzed

ATP + phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P₂) ⇌ ADP + phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P₃) (Burke, 2018; Dbouk et al., 2013; Flanagan & Shepherd, 2014; Whale et al., 2017).

## Cofactor Requirements

Requires a divalent metal ion; Mg²⁺ is preferred, although Mn²⁺ can substitute (Flanagan & Shepherd, 2014; Ilić & Roberts, 2010; Miller et al., 2019).

## Substrate Specificity

Acts primarily as a lipid kinase that most efficiently phosphorylates PtdIns(4,5)P₂. Lower activity toward phosphatidylinositol and phosphatidylinositol-4-phosphate has been reported (Miller et al., 2019). Suggested serine protein-kinase activity is controversial; comprehensive profiling detected no intrinsic protein-kinase activity (Johnson et al., 2023, cited in Brown & Auger, 2011; Burke, 2018).

## Structure

p110β comprises an N-terminal adaptor-binding domain (ABD), Ras-binding domain, C2 domain (containing a nuclear-localization signal), helical domain and C-terminal bilobed kinase domain (Backer, 2011; Rathinaswamy & Burke, 2020). Crystal structure of murine p110β bound to p85β (PDB 2Y3A) reveals a C-terminal helix (Kα12) that folds over the catalytic loop; inhibition is reinforced by the p85 cSH2 domain (Zhang et al., 2011; Miller et al., 2019). An AlphaFold model for human PIK3CB is available (Miller et al., 2019).

## Regulation

Basal activity is inhibited by association with p85 regulatory subunits through contacts from nSH2 to the helical/C2/kinase domains and from cSH2 to the p110β C-terminus (Rathinaswamy & Burke, 2020; Zhang et al., 2011). Activation occurs when p85 SH2 domains bind phosphotyrosine motifs of activated receptor tyrosine kinases, or when p110β directly engages Gβγ subunits or RAC GTPase (Backer, 2011; Burke, 2018). Autophosphorylation on Ser1070 is inhibitory, whereas phosphorylation of p85α on Tyr688 (e.g., by Src or Abl) stimulates activity (Backer, 2011).

## Function

Ubiquitously expressed and localised to cytoplasm and nucleus (Mazloumi Gavgani et al., 2018). Downstream of GPCRs and RTKs, p110β-generated PtdIns(3,4,5)P₃ recruits PH-domain effectors such as AKT and PDK1, driving PI3K/AKT/mTOR signalling involved in cell growth, survival, proliferation and metabolism (Mazloumi Gavgani et al., 2018; Nakanishi et al., 2016). PTEN counteracts this signal (Burke, 2018). Interacting partners include p85, Gβγ, Rab5 and CRKL; the p110β–Rab5 interaction supports a kinase-independent scaffolding role in endocytosis (Backer, 2011). Nuclear pools contribute to DNA replication, cell-cycle progression and DNA repair (Mazloumi Gavgani et al., 2018). Homozygous Pik3cb deletion is embryonic-lethal in mice (Ilić & Roberts, 2010).

## Inhibitors

Isoform-selective inhibitors: GSK2636771, AZD6482, TGX221, KIN-193 (Burke, 2018; Dbouk & Backer, 2013; Miller et al., 2019). Pan-PI3K inhibitors: GDC-0941 (pictilisib) and other dual PI3K/mTOR inhibitors such as BEZ235 (Nakanishi et al., 2016; Pridham et al., 2017).

## Other Comments

p110β is crucial for tumour maintenance in PTEN-deficient cancers; over-expression of wild-type enzyme is oncogenic (Mazloumi Gavgani et al., 2018; Zhao & Vogt, 2008). Activating mutations include E633K (helical) and kinase-domain substitutions D1067Y/V/A, E1051K, L1049R and A1048V, which enhance basal activity and can confer resistance to PI3K inhibitors (Nakanishi et al., 2016; Mazloumi Gavgani et al., 2018). Germline PIK3R1 mutations underlying APDS2 disrupt regulatory control and may indirectly activate p110β (Dornan et al., 2017).

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