## Phylogeny

PTK2B (also called PYK2) is a non-receptor protein-tyrosine kinase that forms, together with FAK (PTK2), a distinct branch within the focal adhesion kinase (FAK) family (Gocek et al., 2014; Han et al., 2009; Naser et al., 2018). The two paralogs arose from a vertebrate gene-duplication event and share ~45–48 % overall sequence identity and ~60–65 % identity within the catalytic domain (Lipinski & Loftus, 2010; Zhu et al., 2018; Pins et al., 2021). Orthologs are present across diverse species, indicating evolutionary conservation of function (Lipinski & Loftus, 2010).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine phosphate (Lipinski & Loftus, 2010; Unknown Author, 2010).

## Cofactor Requirements

Catalytic activity requires a divalent cation, Mg²⁺ or Mn²⁺ (Lipinski & Loftus, 2010; Pins et al., 2021; Zhu et al., 2018).

## Substrate Specificity

PYK2 is an acidophilic tyrosine kinase. It preferentially phosphorylates tyrosine residues flanked by acidic amino acids (Asp/Glu) and favours a hydrophobic residue at the +3 position relative to the phosphotyrosine (Gocek et al., 2014; Han et al., 2009; Yaron-Barir et al., 2024).

## Structure

A 110–125 kDa multi-domain protein comprising (i) an N-terminal FERM domain (subdomains F1-F3) that mediates localization, protein binding and autoinhibition, (ii) a central bi-lobed kinase domain that contains the activation loop (Tyr579/Tyr580) and an atypical DFG motif conformation, and (iii) a C-terminal FAT domain that targets focal adhesions through paxillin binding (Lipinski & Loftus, 2010; Han et al., 2009; Naser et al., 2018). Proline-rich linkers connect the domains. In the inactive state, intramolecular FERM–kinase interactions maintain a closed conformation (Naser et al., 2018; Pins et al., 2021).

## Regulation

Activation is Ca²⁺-dependent. Ca²⁺/calmodulin binding to the FERM domain disrupts autoinhibition, promoting dimerisation and trans-autophosphorylation on Tyr402 (Lipinski & Loftus, 2010; Pins et al., 2021). Phospho-Tyr402 recruits Src-family kinases, which subsequently phosphorylate Tyr579/580 in the activation loop for full activation and Tyr881 in the FAT domain for Grb2 docking (Lipinski & Loftus, 2010; Naser et al., 2018). Dephosphorylation by STEP provides negative regulation (Pins et al., 2021). Unlike FAK, integrin ligation is a minor direct activator; signalling pathways that elevate intracellular Ca²⁺ (e.g., GPCRs) are predominant (Schlaepfer et al., 1999; Lipinski & Loftus, 2010).

## Function

Acts as both a kinase and scaffold to integrate signals regulating cytoskeletal organisation, adhesion, migration, proliferation and apoptosis (Lipinski & Loftus, 2010; Gocek et al., 2014). Expression is enriched in the central nervous system and hematopoietic cells, with cytoplasmic and perinuclear distribution (Gocek et al., 2014). Upstream activators include GPCRs, cytokine/growth-factor receptors, integrins and Ca²⁺ influx (Lipinski & Loftus, 2010; Pins et al., 2021). Key partners/substrates are Src-family kinases, paxillin, Hic-5, p130Cas and the p85 subunit of PI3K, linking PYK2 to PI3K/Akt and MAPK/ERK pathways (Lipinski & Loftus, 2010; Naser et al., 2018; Avraham et al., 2000).

## Inhibitors

Numerous experimental small-molecule inhibitors target the ATP-binding site but often cross-react with FAK owing to active-site conservation. Allosteric compounds directed at the FERM domain and other non-catalytic surfaces are under investigation to improve selectivity (Lipinski & Loftus, 2010; Unknown Author, 2010). The naturally occurring splice variant PRNK, which lacks the kinase domain, functions as an endogenous dominant-negative inhibitor (Lipinski & Loftus, 2010; Zhu et al., 2018).

## Other Comments

Over-expression or dysregulation of PYK2 is linked to cancer progression (glioma, hepatocellular, lung, breast), neurodegenerative diseases (Alzheimer’s, Parkinson’s), psychiatric disorders (stress-induced depression, addiction) and inflammatory pathologies (Lipinski & Loftus, 2010; Pins et al., 2021; Zhu et al., 2018).

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