## Phylogeny

Protein-tyrosine kinase 6 (PTK6, also called Brk) is a non-receptor member of the Tyrosine Kinase (TK) group (Gocek et al., 2014; Ostrander et al., 2010). The Manning classification places it in its own PTK6/Brk family, distinct from but related to Src family kinases; the family also contains FRK and SRMS (Brauer & Tyner, 2009; Tsui & Miller, 2015). A unique exon-intron organization further supports a separate evolutionary lineage (Harvey & Burmi, 2011). PTK6 orthologues are conserved across vertebrates (e.g., mouse Sik) and have been noted in Drosophila (Src42A, Dsrc41) (Ostrander et al., 2010; Zheng & Tyner, 2013).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine phosphate (Yaron-Barir et al., 2024).

## Cofactor Requirements

Catalysis requires a divalent metal ion, usually Mg²⁺ or Mn²⁺ (Yaron-Barir et al., 2024).

## Substrate Specificity

High-throughput profiling classifies PTK6 as an acidophilic tyrosine kinase that prefers acidic residues (Asp/Glu) flanking the target tyrosine (Yaron-Barir et al., 2024). Its SH2 domain recognizes the phosphopeptide motif pY-(D/E)-(D/E)-Y (Brauer & Tyner, 2010).

## Structure

PTK6 is a 451-residue protein comprising an N-terminal SH3 domain, an SH2 domain, and a C-terminal kinase domain (Brauer & Tyner, 2010; Jerin et al., 2023). Absence of N-terminal myristoylation or palmitoylation allows flexible subcellular localization (Brauer & Tyner, 2010; Harvey, 2016). The crystal structure of the isolated kinase domain (PDB 5D7V) shows an inactive “DFG-in/αC-out” conformation in which the Lys-219–Glu-235 salt bridge is absent and Tyr-342 in the activation loop is unphosphorylated (Thakur et al., 2016).

## Regulation

• Phosphorylation – Autophosphorylation of Tyr-342 activates the kinase, whereas phosphorylation of Tyr-447 promotes SH2-mediated autoinhibition; SRMS negatively regulates PTK6, and phosphatases PTP1B and PTEN can dephosphorylate activating sites (Brauer & Tyner, 2010; Jerin et al., 2023).  
• Alternative splicing – The ALT-PTK6 isoform lacks SH2 and kinase domains and acts as a dominant-negative inhibitor (Harvey, 2016; Jerin et al., 2023).  
• Localization – Nuclear PTK6 correlates with growth suppression, while cytoplasmic or membrane localization supports proliferation and survival (Harvey, 2016; Zheng & Tyner, 2013).

## Function

PTK6 modulates differentiation, proliferation, migration and survival in a context-dependent manner (Harvey, 2016; Zheng & Tyner, 2013).  
Expression – Detected in differentiated epithelial cells of the gastrointestinal tract, skin, prostate and breast (Brauer & Tyner, 2010; Zheng & Tyner, 2013).  
Upstream stimuli – Activated downstream of EGF, heregulin and IGF-1 signalling, and of receptor tyrosine kinases EGFR, ERBB2 and MET (Brauer & Tyner, 2010; Jerin et al., 2023).  
Substrates / partners – Phosphorylates AKT, STAT3, STAT5B, β-catenin, paxillin, Sam68 and more than 30 additional proteins; also phosphorylates EGFR at Tyr-845, creating a positive feedback loop (Harvey, 2016; Jerin et al., 2023).  
Pathways – Influences PI3K/AKT, MAPK/ERK5 and STAT signalling cascades (Harvey, 2016).

## Inhibitors

Several experimental ATP-competitive small-molecule inhibitors of the PTK6 kinase domain have been described. They can potentiate chemotherapeutics such as doxorubicin or paclitaxel in some models but have not reduced breast-tumour growth in vivo; no SH2-directed inhibitors are known (Dwyer et al., 2021; Harvey, 2016; Jerin et al., 2023).

## Other Comments

PTK6 is overexpressed in 60–85 % of invasive ductal breast carcinomas and in prostate, colon and ovarian cancers, where high levels often correlate with poor prognosis. In prostate cancer, nuclear-to-cytoplasmic relocalization promotes tumour progression. Somatic PTK6 mutations are rare but have been reported in melanoma (Brauer & Tyner, 2010; Harvey, 2016; Zheng & Tyner, 2013).

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