## Phylogeny

According to the comprehensive classification of the human kinome, Protein-tyrosine kinase 6 (PTK6/Brk) is a non-receptor tyrosine kinase belonging to the Tyrosine Kinase (TK) group (ostrander2010brkptk6signalingin pages 8-9, tsui2015cancerassociatedmutationsin pages 14-16, gocek2014nonreceptorproteintyrosine pages 3-4). The Manning et al. 2002 Science paper assigns PTK6 to a distinct family, the PTK6/Brk family, which is phylogenetically related to but separate from the canonical Src family (gocek2014nonreceptorproteintyrosine pages 3-4, ostrander2010brkptk6signalingin pages 7-8, brauer2009rakinginakt pages 5-6). This family also includes the kinases FRK (Fyn-related kinase) and SRMS (SRC-related kinase lacking certain regulatory sites) (tsui2015cancerassociatedmutationsin pages 11-13, zheng2013context‐specificproteintyrosine pages 1-2). The distinct evolutionary lineage of the PTK6 family is supported by its unique exon-intron gene structure (harvey2011futuretherapeuticstrategies pages 18-20, zheng2013context‐specificproteintyrosine pages 1-2). PTK6 is conserved in vertebrates, with known orthologs including the mouse ortholog Sik (Src-related intestinal kinase), and the Drosophila kinases Src42A and Dsrc41 (ostrander2010brkptk6signalingin pages 7-8, tsui2015cancerassociatedmutationsin pages 11-13, unknownauthors2019thepotentialand pages 36-41, zheng2013context‐specificproteintyrosine pages 1-2).

## Reaction Catalyzed

ATP + a [protein]-L-tyrosine = ADP + a [protein]-L-tyrosine phosphate (yaronbarir2024theintrinsicsubstrate pages 1-2, yaronbarir2024theintrinsicsubstrate pages 16-17).

## Cofactor Requirements

The catalytic activity of PTK6 requires divalent metal ion cofactors, typically Mg²⁺ or Mn²⁺, to facilitate ATP binding and catalysis (yaronbarir2024theintrinsicsubstrate pages 1-2, yaronbarir2024theintrinsicsubstrate pages 2-2).

## Substrate Specificity

Based on high-throughput profiling of the human tyrosine kinome, PTK6 is classified as an acidophilic kinase (yaronbarir2024theintrinsicsubstrate pages 2-3). Its consensus substrate motif is characterized by a strong preference for negatively charged acidic residues, such as aspartic acid (Asp) or glutamic acid (Glu), flanking the target tyrosine phosphorylation site (yaronbarir2024theintrinsicsubstrate pages 2-3). The PTK6 SH2 domain, which mediates protein-protein interactions, recognizes a distinct phosphopeptide motif of pY-(D/E)-(D/E)-Y (brauer2010buildingabetter pages 2-2).

## Structure

PTK6 is a 451 amino acid protein that contains an N-terminal SH3 domain, an SH2 domain, and a C-terminal kinase domain (brauer2010buildingabetter pages 2-2, jerin2023therapeuticpotentialof pages 2-4). The SH3 and SH2 domains mediate protein-protein interactions and autoregulation (brauer2010buildingabetter pages 2-2). Unlike Src family kinases, PTK6 lacks N-terminal myristoylation or palmitoylation signals, affording it flexible subcellular localization (brauer2010buildingabetter pages 2-2, harvey2016proteintyrosinekinase6 pages 1-5). The crystal structure of the human PTK6 kinase domain (PDB: 5D7V) shows the kinase in an inactive conformation described as “DFG-in” and “αC-helix-out” (thakur2016crystalstructureof pages 1-2, thakur2016crystalstructureof pages 3-4, thakur2016crystalstructureof pages 4-5). In this state, the αC-helix is displaced outward, preventing the formation of a critical salt bridge between the catalytic residues Lys-219 and Glu-235 (thakur2016crystalstructureof pages 3-4). The activation loop is unphosphorylated at Tyr-342, which is consistent with an inactive kinase (thakur2016crystalstructureof pages 3-4, thakur2016crystalstructureof pages 4-5).

## Regulation

PTK6 activity is regulated by phosphorylation, intramolecular interactions, alternative splicing, and subcellular localization (jerin2023therapeuticpotentialof pages 2-4). - **Phosphorylation**: PTK6 autophosphorylates at several sites. Phosphorylation of Tyr-342 within the activation loop is a key activating event (brauer2010buildingabetter pages 2-2, jerin2023therapeuticpotentialof pages 2-4). Conversely, phosphorylation of Tyr-447 in the C-terminal tail promotes an intramolecular interaction with the SH2 domain, leading to autoinhibition (brauer2010buildingabetter pages 2-2, jerin2023therapeuticpotentialof pages 2-4). The kinase SRMS acts as a negative regulator, while the phosphatases PTP1B and PTEN can dephosphorylate PTK6 activating sites (jerin2023therapeuticpotentialof pages 6-8). - **Alternative Splicing**: An alternatively spliced isoform, ALT-PTK6, lacks the SH2 and kinase domains but retains the SH3 domain (harvey2016proteintyrosinekinase6 pages 1-5, jerin2023therapeuticpotentialof pages 2-4). ALT-PTK6 functions as a competitive inhibitor of full-length PTK6 (jerin2023therapeuticpotentialof pages 2-4, unknownauthors2019thepotentialand pages 36-41). - **Localization**: PTK6 function is compartmentalized. Nuclear localization is associated with growth suppression, while localization to the cytoplasm and plasma membrane promotes proliferation and survival (harvey2016proteintyrosinekinase6 pages 1-5, zheng2013context‐specificproteintyrosine pages 1-2).

## Function

PTK6 is a non-receptor tyrosine kinase that regulates cellular processes including differentiation, proliferation, migration, and survival in a context-dependent manner (harvey2016proteintyrosinekinase6 pages 5-9, zheng2013context‐specificproteintyrosine pages 1-2). - **Expression**: PTK6 is expressed in differentiated epithelial cells of the gastrointestinal tract, skin, prostate, and breast (brauer2010buildingabetter pages 3-4, zheng2013context‐specificproteintyrosine pages 1-2). - **Signaling Partners**: Activation is stimulated by signals including EGF, heregulin, and IGF-1 (brauer2010buildingabetter pages 3-4). It functions downstream of receptor tyrosine kinases like EGFR, ERBB2, and MET (jerin2023therapeuticpotentialof pages 6-8). PTK6 interacts with and phosphorylates over 35 substrates, including AKT, STAT3, STAT5b, β-catenin, paxillin, and Sam68 (harvey2016proteintyrosinekinase6 pages 1-5, brauer2010buildingabetter pages 2-2). It creates a positive feedback loop by phosphorylating EGFR at residue Y845, which enhances EGFR signaling (jerin2023therapeuticpotentialof pages 6-8). - **Pathways**: PTK6 modulates key signaling pathways such as PI3K/Akt, MAPK/Erk5, and STAT signaling (harvey2016proteintyrosinekinase6 pages 5-9, harvey2016proteintyrosinekinase6 pages 9-14).

## Inhibitors

Several experimental small-molecule inhibitors targeting the ATP-binding pocket of the PTK6 kinase domain have been developed (harvey2016proteintyrosinekinase6 pages 9-14, dwyer2021breasttumorkinase pages 12-13). In some cancer models, these inhibitors can enhance the effects of chemotherapies like doxorubicin and paclitaxel; however, they have failed to reduce tumorigenesis in breast cancer models (jerin2023therapeuticpotentialof pages 6-8, dwyer2021breasttumorkinase pages 12-13). There are currently no known inhibitors that specifically target the PTK6 SH2 domain (dwyer2021breasttumorkinase pages 12-13).

## Other Comments

PTK6 is frequently overexpressed in various cancers, including 60-85% of invasive ductal breast carcinomas, as well as prostate, colon, and ovarian tumors, where its expression often correlates with tumor progression and poor prognosis (brauer2010buildingabetter pages 3-4, harvey2016proteintyrosinekinase6 pages 5-9, unknownauthors2019thepotentialand pages 36-41). Its role is context-dependent; in normal tissues, it often promotes differentiation and negatively regulates proliferation (zheng2013context‐specificproteintyrosine pages 1-2). In prostate cancer, translocation of PTK6 from the nucleus to the cytoplasm and membrane compartments facilitates tumor progression (zheng2013context‐specificproteintyrosine pages 1-2). Somatic mutations in PTK6 have been identified in melanomas, but these are rare in breast cancer (brauer2010buildingabetter pages 3-4).

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