## Phylogeny

PTK2 (focal-adhesion kinase, FAK) is a member of the tyrosine-kinase (TK) group and, together with its vertebrate paralogue PTK2B/PYK2, forms the focal-adhesion kinase sub-family (Unknown Authors, 2008). Orthologues are found throughout Metazoa, including Mus musculus Ptk2, Rattus norvegicus Ptk2, Danio rerio ptk2a/ptk2b, Drosophila melanogaster FAK56D and Caenorhabditis elegans ptk-1 (Angelucci & Bologna, 2007; Unknown Authors, 2025).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇄ ADP + [protein]-O-phospho-L-tyrosine (Lietha et al., 2007).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and catalytic activity (Le Coq et al., 2022; Shanthi et al., 2014).

## Substrate Specificity

Peptide-array profiling defines an acidophilic consensus D/E-x-pY-D/E, indicating preference for acidic residues flanking the phosphotyrosine (Yaron-Barir et al., 2024). Verified cellular substrates include paxillin, p130Cas/BCAR1 and VE-cadherin (Yaron-Barir et al., 2024; Kleinschmidt & Schlaepfer, 2017; Angelucci & Bologna, 2007).

## Structure

FAK contains an N-terminal FERM domain (lobes F1–F3), a linker with autophosphorylation site Tyr397, a bilobal kinase domain bearing activation-loop Tyr576/Tyr577, three proline-rich motifs, and a C-terminal four-helix FAT domain (Lietha et al., 2007; Panera et al., 2017; Le Coq et al., 2022).  
• Autoinhibited structures (PDB 2J0J/2J0L) show the FERM-F2 lobe docked on the kinase C-lobe, occluding the active site and sequestering Tyr397 ~35 Å away (Lietha et al., 2007).  
• An active, phosphorylated conformation (PDB 4NY0) features a β-hairpin activation loop stabilized by pTyr577, incompatible with FERM docking (Lietha et al., 2007).  
• The C-helix remains in an active orientation; regulation relies on FERM-kinase contacts rather than C-helix displacement (Lietha et al., 2007).  
• PI(4,5)P₂ binds basic surfaces on FERM and kinase domains, positioning the autoinhibited enzyme at membranes without fully relieving inhibition (Le Coq et al., 2022).  
• FERM:FERM and FAT:FAT interfaces promote dimerization that enables trans-autophosphorylation at Tyr397 (Brami-Cherrier et al., 2014; Le Coq et al., 2022).

## Regulation

Autophosphorylation of Tyr397 generates an SH2 docking site for SRC, PI3K-p85 and GRB7 (Angelucci & Bologna, 2007). SRC subsequently phosphorylates Tyr576/Tyr577 (full activation) and Tyr861/Tyr925 (signal propagation) (Angelucci & Bologna, 2007; Mousson et al., 2018).  
SUMOylation of Lys152 enhances Tyr397 autophosphorylation (Mousson et al., 2018).  
MDM2 and Cbl ubiquitinate FAK, targeting it for proteasomal degradation (Shanthi et al., 2014; Chuang et al., 2022).  
PTP-PEST dephosphorylates Tyr397, dampening activity (Shanthi et al., 2014).  
Intramolecular FERM-kinase docking enforces autoinhibition; release is promoted by PI(4,5)P₂ binding, mechanical force via vinculin-paxillin linkages and dimerization-driven trans-phosphorylation (Le Coq et al., 2022; Kleinschmidt & Schlaepfer, 2017; Brami-Cherrier et al., 2014).

## Function

FAK is highly expressed in endothelial and smooth-muscle cells, osteoclasts and fibroblasts, and is frequently over-expressed or amplified in breast, ovarian and hepatocellular carcinomas (Angelucci & Bologna, 2007; Rigiracciolo et al., 2021; Panera et al., 2017).  
Upstream activators include integrins, EGFR/PDGFR, GPCRs, VEGF and extracellular matrix stiffness, all converging on FERM displacement and Tyr397 autophosphorylation (Angelucci & Bologna, 2007; Kleinschmidt & Schlaepfer, 2017; Le Coq et al., 2022).  
Downstream, the FAK–SRC complex phosphorylates paxillin, p130Cas and PLC-γ1, recruiting GRB2 and PI3K to stimulate Rac/Cdc42, ERK, JNK and PI3K-Akt pathways (Angelucci & Bologna, 2007; Kleinschmidt & Schlaepfer, 2017).  
At adherens junctions FAK phosphorylates VE-cadherin Tyr658 and β-catenin Tyr142, regulating vascular permeability (Kleinschmidt & Schlaepfer, 2017).  
The nuclear FERM domain associates with MDM2 to accelerate p53 ubiquitination and promote cell survival (Tan et al., 2023; Lu & Sun, 2020).  
Genetic ablation causes embryonic lethality with severe vascular defects, highlighting essential roles in angiogenesis, cardiogenesis and neurodevelopment (Angelucci & Bologna, 2007).  
The FRNK splice variant acts as a dominant-negative inhibitor at focal adhesions (Angelucci & Bologna, 2007).

## Inhibitors

Potent ATP-competitive inhibitors include defactinib (VS-6063, IC₅₀ ≈ 0.6 nM), PF-573228 (IC₅₀ 0.1–5 µM), TAE226 (IC₅₀ ≈ 6.8 nM), GSK2256098 (IC₅₀ ≈ 1.5 nM) and PND-1186/VS-4718 (IC₅₀ ≈ 100 nM) (Aakriti et al., 2025; Mousson et al., 2018; Sulzmaier et al., 2014; Chuang et al., 2022).

## Other Comments

PTK2 amplification or over-expression correlates with poor prognosis in lung, liver, gastric, colorectal, breast and ovarian cancers (Zhang et al., 2022; Rigiracciolo et al., 2021). FAK inhibition diminishes fibrosis and improves immune infiltration in stiff tumour microenvironments such as pancreatic ductal adenocarcinoma (Kleinschmidt & Schlaepfer, 2017).

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