## Phylogeny

PTK2 belongs to the tyrosine-kinase (TK) group and constitutes the focal-adhesion kinase sub-family together with its vertebrate paralog PTK2B/PYK2 (unknownauthors2008achemicalbiologyapproach pages 27-30).  
Orthologs are conserved across metazoans: Mus musculus Ptk2, Rattus norvegicus Ptk2, Danio rerio ptk2a and ptk2b, Drosophila melanogaster FAK56D, and Caenorhabditis elegans ptk-1 (angelucci2007targetingvascularcell pages 12-13, unknownauthors2025fromactivityinference pages 75-75).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate (lietha2007structuralbasisfor pages 2-3).

## Cofactor Requirements

Catalytic activity requires Mg²⁺ for ATP coordination (coq2022newinsightsinto pages 2-2, shanthi2014focaladhesionkinase pages 23-24).

## Substrate Specificity

Intrinsic peptide-array profiling defines an acidophilic consensus motif D/E-x-pY-D/E, indicating preference for acidic residues flanking the phosphorylated tyrosine (yaronbarir2024theintrinsicsubstrate pages 2-3, yaronbarir2024theintrinsicsubstrate pages 16-16).  
Validated cellular substrates include paxillin, p130Cas/BCAR1 and VE-cadherin (yaronbarir2024theintrinsicsubstrate pages 5-5, kleinschmidt2017focaladhesionkinase pages 4-6, angelucci2007targetingvascularcell pages 6-7).

## Structure

FAK comprises an N-terminal FERM domain (lobes F1–F3), a linker containing the autophosphorylation site Tyr397, a bilobal kinase domain with activation-loop Tyr576/Tyr577, three proline-rich motifs, and a C-terminal four-helix FAT domain (lietha2007structuralbasisfor pages 1-2, panera2017focaladhesionkinase pages 1-3, coq2022newinsightsinto pages 2-4).  
Autoinhibited structures 2J0J/2J0L show the FERM F2 lobe docking onto the kinase C-lobe, occluding the active site and burying Tyr397 ~35 Å away (lietha2007structuralbasisfor pages 2-3).  
Structure 4NY0 of the phosphorylated kinase reveals a β-hairpin activation loop stabilized by pTyr577, incompatible with FERM binding and representative of the active state (lietha2007structuralbasisfor pages 7-8).  
The C-helix remains in an active orientation; regulation depends on FERM-kinase contacts rather than C-helix displacement (lietha2007structuralbasisfor pages 3-5).  
PI(4,5)P₂ engages basic patches in FERM and kinase domains, orienting the autoinhibited enzyme against the membrane without fully relieving inhibition (coq2022newinsightsinto pages 2-4).  
FERM:FERM and FAT:FAT interfaces drive dimerization that enables trans-autophosphorylation at Tyr397 (bramicherrier2014fakdimerizationcontrols pages 1-2, coq2022newinsightsinto pages 6-7).

## Regulation

Autophosphorylation at Tyr397 creates an SH2 docking site for SRC, PI3K-p85 and GRB7 (angelucci2007targetingvascularcell pages 3-4).  
SRC subsequently phosphorylates Tyr576/Tyr577 (full catalytic activation) and Tyr861/Tyr925 (signal propagation) (angelucci2007targetingvascularcell pages 5-6, mousson2018targetingfocaladhesion pages 9-11).  
SUMOylation of Lys152 within the FERM domain increases Tyr397 phosphorylation (mousson2018targetingfocaladhesion pages 9-11).  
MDM2 and Cbl ubiquitinate FAK, targeting it for proteasomal degradation (shanthi2014focaladhesionkinase pages 23-24, chuang2022fakincancer pages 14-16).  
PTP-PEST dephosphorylates Tyr397, attenuating activity (shanthi2014focaladhesionkinase pages 23-24).  
FERM-kinase intramolecular docking enforces autoinhibition; release is promoted by PI(4,5)P₂ binding, mechanical force transmitted via vinculin–paxillin linkages, and dimerization-induced trans-phosphorylation (coq2022newinsightsinto pages 6-7, kleinschmidt2017focaladhesionkinase pages 10-13, bramicherrier2014fakdimerizationcontrols pages 1-2).

## Function

FAK is highly expressed in endothelial and smooth-muscle cells, osteoclasts, fibroblasts, and is frequently over-expressed or amplified in breast, ovarian and hepatocellular carcinomas (angelucci2007targetingvascularcell pages 6-7, rigiracciolo2021focaladhesionkinase pages 2-4, panera2017focaladhesionkinase pages 1-3).  
Upstream activators include integrins, EGFR/PDGFR, GPCRs, VEGF and matrix stiffness, all converging on FERM displacement and Tyr397 autophosphorylation (angelucci2007targetingvascularcell pages 5-6, kleinschmidt2017focaladhesionkinase pages 9-10, coq2022newinsightsinto pages 2-4).  
Downstream, the FAK-SRC complex phosphorylates paxillin, p130Cas and PLC-γ1, recruiting GRB2 and PI3K to trigger Rac/Cdc42, ERK, JNK and PI3K-Akt cascades (angelucci2007targetingvascularcell pages 5-6, kleinschmidt2017focaladhesionkinase pages 4-6).  
At adherens junctions FAK phosphorylates VE-cadherin Tyr658 and β-catenin Tyr142, modulating vascular permeability (kleinschmidt2017focaladhesionkinase pages 4-6).  
Nuclear FERM interacts with MDM2, accelerating p53 ubiquitination and promoting survival (tan2023focaladhesionkinase pages 1-2, lu2020progressinthe pages 1-2).  
Genetic ablation causes embryonic lethality with severe vascular defects, underscoring roles in angiogenesis, cardiogenesis and neuronal development (angelucci2007targetingvascularcell pages 6-7).  
FAK links extracellular matrix stiffness to cyclin D1 expression and cell-cycle progression via Rac activation (kleinschmidt2017focaladhesionkinase pages 9-10).  
The FRNK isoform acts as a dominant-negative regulator occupying focal adhesions and suppressing FAK phosphorylation (angelucci2007targetingvascularcell pages 3-4).

## Inhibitors

Defactinib (VS-6063) IC₅₀ ≈ 0.6 nM versus Tyr397 autophosphorylation (aakriti2025focaladhesionkinase pages 8-10).  
PF-573228 blocks ATP binding with IC₅₀ 0.1–5 µM (aakriti2025focaladhesionkinase pages 8-10).  
TAE226 inhibits FAK/IGF-IR with IC₅₀ ≈ 6.8 nM (aakriti2025focaladhesionkinase pages 8-10, mousson2018targetingfocaladhesion pages 9-11).  
GSK2256098 is a reversible inhibitor with IC₅₀ ≈ 1.5 nM and pronounced anti-angiogenic activity (aakriti2025focaladhesionkinase pages 8-10, sulzmaier2014fakincancer pages 29-30).  
PND-1186 (VS-4718) is orally bioavailable, inducing apoptosis with IC₅₀ ≈ 100 nM (aakriti2025focaladhesionkinase pages 8-10, chuang2022fakincancer pages 26-28).

## Other Comments

PTK2 amplification or over-expression correlates with aggressive behaviour and poor prognosis in lung, liver, gastric, colorectal, breast and ovarian cancers (zhang2022functionalandclinical pages 1-2, rigiracciolo2021focaladhesionkinase pages 2-4).  
FAK inhibition reduces fibrosis and enhances immune infiltration in stiff tumour microenvironments such as pancreatic ductal adenocarcinoma (kleinschmidt2017focaladhesionkinase pages 9-10).

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