## Phylogeny

• Member of cytoplasmic tyrosine-kinase group IV (FES/FER family) within the human kinome (craig2012fesferkinasesignaling pages 1-3).  
• Single human paralog FER; a testis-restricted FER splice variant is FERT (craig2012fesferkinasesignaling pages 1-3).  
• Orthologs in Mus musculus, Danio rerio, Gallus gallus (viral v-Fes), Felis catus (viral v-Fps) and Drosophila melanogaster, indicating conservation from insects to mammals (craig2012fesferkinasesignaling pages 1-3).  
• SH2-kinase coupling architecture is most related to the ABL family yet distinct from Src/Tec/Csk branches (filippakopoulos2008structuralcouplingof pages 4-5).

## Reaction Catalyzed

protein-L-tyrosine + ATP ⇌ protein-L-tyrosine-O-phosphate + ADP (filippakopoulos2008structuralcouplingof pages 4-5, hellwig2012smallmoleculeinhibitorsof pages 1-2).

## Cofactor Requirements

Requires ATP and divalent cations, with Mg²⁺ preferred over Mn²⁺ (craig2012fesferkinasesignaling pages 3-4, filippakopoulos2008structuralcouplingof pages 4-5).

## Substrate Specificity

• Peptide library profiling shows preference for a bulky aliphatic residue at –1, an acidic or phosphorylated residue at +1, and a hydrophobic residue at +3 relative to the acceptor tyrosine, summarised as Φ-Y-[D/E/pS/pT]-x-Φ (filippakopoulos2008structuralcouplingof pages 4-5).  
• Confirmed cellular substrates following this pattern include cortactin and p120-catenin (filippakopoulos2008structuralcouplingof pages 4-5).

## Structure

• Domain order: N-terminal F-BAR (FCH + coiled-coil) → FX extension → SH2 → kinase domain (craig2012fesferkinasesignaling pages 3-4).  
• F-BAR forms crescent-shaped homodimers that bind PI(4,5)P₂; mutation L145P disrupts dimerisation and increases activity (craig2012fesferkinasesignaling pages 3-4).  
• Crystal structure of SH2-kinase fragment (PDB 4E93) displays SH2 packed against the N-lobe, stabilising the αC-helix and an ordered activation loop containing Tyr713 (filippakopoulos2008structuralcouplingof pages 4-5).  
• Gatekeeper Met639 controls ATP-binding pocket dimensions and inhibitor class sensitivity (hellwig2012smallmoleculeinhibitorsof pages 4-5).  
• SH2 NMR solution structure reveals a distinctive negative surface potential, explaining absence of Src-like autoinhibition (scott2005solutionstructureof pages 5-5).

## Regulation

• Autoinhibition via F-BAR-mediated oligomerisation; binding to phosphoinositide-rich membranes disengages this restraint (craig2012fesferkinasesignaling pages 3-4).  
• Autophosphorylation on Tyr713 is essential for catalytic activation (hellwig2012smallmoleculeinhibitorsof pages 1-2).  
• SH2 domain engagement with phosphotyrosine ligands further stabilises the active state (filippakopoulos2008structuralcouplingof pages 4-5).  
• Tyrosine phosphatases SHP-1 (PTPN6) and SHP-2 (PTPN11) negatively regulate signalling (craig2012fesferkinasesignaling pages 14-15).  
• Promoter CpG methylation diminishes expression in colorectal carcinoma (hellwig2012smallmoleculeinhibitorsof pages 2-4).  
• Activating L145P mutation within F-BAR augments membrane targeting and oncogenic potential (craig2012fesferkinasesignaling pages 3-4).

## Function

• Highly expressed in hematopoietic progenitors, neutrophils, mast cells and macrophages; also present in endothelial, epithelial and neuronal tissues (craig2012fesferkinasesignaling pages 1-3, hellwig2012smallmoleculeinhibitorsof pages 1-2).  
• Activated downstream of FcεRI and KIT in mast cells; also transmits oncogenic KIT^D816V and FLT3-ITD signals in AML (craig2012fesferkinasesignaling pages 1-3, craig2012fesferkinasesignaling pages 14-15).  
• Verified substrates and partners:  
– SYK Y352, HS1 Y397 and PLCγ2 during neutrophil phagocytosis (wel2020chemicalgeneticsstrategy pages 15-15).  
– Cortactin, tubulin, plectin for cytoskeletal control (filippakopoulos2008structuralcouplingof pages 4-5).  
– BCR and NSF in receptor signalling and vesicle fusion (craig2012fesferkinasesignaling pages 8-9).  
• Biological roles:  
– Drives actin remodelling and phagosome formation required for bacterial uptake (wel2020chemicalgeneticsstrategy pages 15-15).  
– Regulates mast-cell degranulation downstream of FcεRI/KIT (craig2012fesferkinasesignaling pages 1-3).  
– Promotes myeloid differentiation in K562 cells and primary progenitors (yates1996roleofc‐fes pages 7-7).  
– Essential for M-CSF/RANKL-dependent osteoclastogenesis (hellwig2012smallmoleculeinhibitorsof pages 8-9).  
– Facilitates endothelial migration and angiogenic tube formation in response to FGF-2, VEGF-A and Ang1/2 (hellwig2012smallmoleculeinhibitorsof pages 2-4).

## Inhibitors

• TAE684 – type I, IC₅₀ ≈ 0.12 µM; co-crystal structure available (hellwig2012smallmoleculeinhibitorsof pages 4-5).  
• WZ-4-49-1 and WZ-4-49-8 – pyrazolopyrimidine type I inhibitors, IC₅₀ ≈ 0.07 µM, high selectivity (hellwig2012smallmoleculeinhibitorsof pages 4-5).  
• HG-7-27-01 and HG-7-92-01 – type II inhibitors, sub-micromolar potency (hellwig2012smallmoleculeinhibitorsof pages 4-5).  
• WEL028 – covalent probe for engineered Cys-mutant FES, blocks SYK phosphorylation and phagocytosis (wel2020chemicalgeneticsstrategy pages 15-15).  
• Dual FES/FLT3 inhibition markedly suppresses FLT3-ITD⁺ AML cell growth (weir2017dualinhibitionof pages 18-19).

## Other Comments

• Displays context-dependent behaviour: kinase-activating mutants transform fibroblasts, whereas epigenetic silencing accelerates colorectal and breast tumourigenesis (hellwig2012smallmoleculeinhibitorsof pages 2-4).  
• Gatekeeper Met639 is a primary determinant of inhibitor specificity (hellwig2012smallmoleculeinhibitorsof pages 4-5).  
• Activating F-BAR mutation L145P enhances kinase activity by destabilising autoinhibitory oligomers (craig2012fesferkinasesignaling pages 3-4).

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