## Phylogeny

Human Fgr (SRC2) is a cytoplasmic non-receptor tyrosine kinase within the Src family of the TK group of the human kinome (shen2018thesrcfamily pages 1-2, hunter2015theeukaryoticprotein pages 3-6).  
Orthologs are conserved across vertebrates; the murine c-Fgr protein shares ~85 % overall and 92 % C-terminal identity with the human enzyme, reflecting strong evolutionary conservation of catalytic and regulatory domains (unknownauthors1995expressionofthe pages 25-28).  
Phylogenetically, Fgr clusters with Src, Yes, Fyn, Lyn, Hck, Lck and Blk, arising from early gene duplication events in vertebrate evolution (link1995theprotooncogenecfgr pages 3-3).

## Reaction Catalyzed

Protein-L-tyrosine + ATP → Protein-L-tyrosine-phosphate + ADP + H⁺ (du2022atpsiteinhibitorsinduce pages 1-3, shen2018thesrcfamily pages 1-2).

## Cofactor Requirements

Not explicitly reported in the cited literature.

## Substrate Specificity

A global consensus motif has not been delineated. Experimentally, Fgr phosphorylates ITAM-containing substrates such as the FcεRI γ-chain and the kinase Syk, implying tolerance for YxxL/I contexts (lee2011thesrcfamily pages 5-6). In vitro peptide studies show preference for sequences surrounding its own activation loop Tyr400 (KDDEYNPA) over the C-terminal tail peptide EPQYQPA (ruzzene1994regulationofcfgr pages 4-6).

## Structure

Domain organisation: N-terminal myristoylated unique segment (removed in recombinant constructs), SH3 (residues 77–138), SH2 (144–241), SH2–kinase linker, bilobed kinase domain (263–516) and C-terminal regulatory tail (527–530) (du2022atpsiteinhibitorsinduce pages 11-13).  
Crystallography:  
• SH3 domain, 1.93 Å, PDB 7JT9, space group I222 (perez2022amodelfor pages 27-28).  
• Near-full-length Fgr:A-419259, 2.55 Å, PDB 7UY0; closed Src-like conformation with SH3 bound to PPII linker and SH2 engaged with pTyr527 tail (du2022atpsiteinhibitorsinduce pages 14-18).  
• Near-full-length Fgr:TL02-59, 2.99 Å, PDB 7UY3; SH3 and SH2 released, kinase adopts DFG-out/αC-in type II state (du2022atpsiteinhibitorsinduce pages 18-23).  
Key catalytic/regulatory elements: Lys295–Glu310 ion pair, DFG motif (Asp404) toggle, gatekeeper Thr338, activation-loop Tyr416. A distinctive Asn-Pro-Cys (NPC) motif replaces the TAR sequence of other SFKs, preventing α-helix formation in the inactive loop and favouring an extended, solvent-exposed Tyr416 (shen2018thesrcfamily pages 6-6). Crystal packing reveals dimers orienting one activation loop into the partner’s active site, explaining trans-autophosphorylation (du2022atpsiteinhibitorsinduce pages 5-6).

## Regulation

Phosphorylation  
• Tyr416 (activation loop): autophosphorylation; activates catalytic activity (shen2018thesrcfamily pages 6-7).  
• Tyr527 (C-terminal tail): phosphorylated by C-terminal Src kinase (CSK); forms SH2 interaction yet fails to suppress Fgr activity, contrasting with other SFKs (ruzzene1994regulationofcfgr pages 4-6, shen2018thesrcfamily pages 2-3).  
• Dual phosphorylation (Tyr400/Tyr511 in c-Fgr numbering) is promoted by polycationic effectors, with Tyr400 overriding the inhibitory effect of Tyr511 (ruzzene1994regulationofcfgr pages 6-7).

Allosteric and conformational control  
Canonical SH3-linker and SH2-tail interactions assemble a closed conformation, but Fgr retains high basal activity even when these contacts are intact, indicating weakened allosteric coupling (shen2018thesrcfamily pages 3-3). Binding of ATP-site inhibitors elicits large-scale repositioning of SH3 and SH2 domains, demonstrating drug-induced allostery (du2022atpsiteinhibitorsinduce pages 18-23).

## Function

Expression: Predominantly in myeloid hematopoietic cells—neutrophils, monocytes, macrophages and mast cells—as well as mantle zone B lymphocytes (lee2011thesrcfamily pages 1-2, link1995theprotooncogenecfgr pages 3-3).  
Upstream receptors: FcεRI, FcγR, integrins ITGB1/ITGB2 (lee2011thesrcfamily pages 6-7).  
Downstream signalling: Enhances phosphorylation and activation of Syk, LAT, SLP76, Gab2, Akt, ERK1/2, p38 and JNK, driving degranulation, cytokine and leukotriene production in mast cells (lee2011thesrcfamily pages 5-6). In AML cells, constitutive Fgr activity supports proliferation and transformation independent of SH3-SH2 regulation (shen2018thesrcfamily pages 6-7).  
Cellular roles: Promotes mast-cell degranulation and IgE-mediated anaphylaxis; modulates cytoskeletal rearrangement, adhesion and migration in neutrophils and macrophages; context-dependent negative feedback on ITGB2-mediated phagocytosis (lee2011thesrcfamily pages 7-8).

## Inhibitors

A-419259: type I, αC-out/DFG-in inhibitor that stabilises the closed conformation (du2022atpsiteinhibitorsinduce pages 6-8).  
TL02-59: type II, αC-in/DFG-out inhibitor that displaces SH3 and SH2 domains, producing an open allosteric state (du2022atpsiteinhibitorsinduce pages 18-23).

## Other Comments

Disease links: Over-expression and constitutive activation in acute myeloid leukaemia (AML) (shen2018thesrcfamily pages 1-2). SH3-domain cancer mutations cluster in RT and distal loops, potentially perturbing regulatory interactions (perez2022amodelfor pages 27-28). Fgr knock-down attenuates passive cutaneous anaphylaxis in mice, highlighting therapeutic potential in allergic disorders (lee2011thesrcfamily pages 8-9).

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