Phylogeny  
Fgr is a cytoplasmic non-receptor tyrosine kinase of the Src family within the tyrosine-kinase (TK) group of the human kinome (Shen et al., 2018; Hunter & Manning, 2015). Orthologs are conserved throughout vertebrates; mouse c-Fgr shares ~85 % overall and 92 % C-terminal sequence identity with the human enzyme, underscoring strong conservation of catalytic and regulatory regions (Unknown authors, 1995). Within the Src-family phylogram, Fgr clusters with Src, Yes, Fyn, Lyn, Hck, Lck and Blk, reflecting early gene-duplication events in vertebrate evolution (Link & Zutter, 1995).

Reaction Catalyzed  
Protein-L-tyrosine + ATP ⇌ Protein-L-tyrosine-phosphate + ADP + H⁺ (Du et al., 2022; Shen et al., 2018).

Cofactor Requirements  
Not reported in the cited literature.

Substrate Specificity  
A universal consensus motif has not been defined. Fgr phosphorylates ITAM-containing substrates such as the FcεRI γ-chain and Syk, indicating tolerance for YxxL/I contexts (Lee et al., 2011). Peptide studies show higher activity toward the activation-loop sequence KDDEYNPA (Tyr400) than toward the C-terminal tail peptide EPQYQPA (Ruzzene et al., 1994).

Structure  
Domain architecture: N-terminal myristoylated unique segment, SH3 (res. 77–138), SH2 (144–241), SH2-kinase linker, bilobed kinase domain (263–516), and C-terminal regulatory tail (527–530) (Du et al., 2022).  
Crystal structures:  
• SH3 domain, 1.93 Å (PDB 7JT9) (Pérez et al., 2022).  
• Near-full-length Fgr bound to A-419259, 2.55 Å, closed Src-like state (PDB 7UY0) (Du et al., 2022).  
• Near-full-length Fgr bound to TL02-59, 2.99 Å, open DFG-out/αC-in state (PDB 7UY3) (Du et al., 2022).  
Key elements include the Lys295–Glu310 ion pair, DFG motif (Asp404), gatekeeper Thr338 and activation-loop Tyr416. An Asn-Pro-Cys (NPC) sequence replaces the canonical TAR motif, keeping Tyr416 solvent-exposed and favoring an extended inactive-loop conformation (Shen et al., 2018). Crystal packing reveals dimers in which one activation loop projects into the partner active site, rationalising trans-autophosphorylation (Du et al., 2022).

Regulation  
Phosphorylation  
• Tyr416 (activation loop): autophosphorylation enhances activity (Shen et al., 2018).  
• Tyr527 (C-terminal tail): phosphorylated by C-terminal Src kinase (CSK); unlike other SFKs, this modification does not fully suppress Fgr catalytic output (Ruzzene et al., 1994; Shen et al., 2018).  
• Dual Tyr400/Tyr511 phosphorylation, promoted by polycationic effectors, shows Tyr400-mediated relief of Tyr511 inhibition (Ruzzene et al., 1994).

Allosteric control  
Canonical SH3-linker and SH2-tail contacts can generate a closed conformation, yet Fgr retains unusually high basal activity, indicating weakened inter-domain coupling (Shen et al., 2018). ATP-site inhibitors drive large SH3/SH2 relocalisation, demonstrating drug-induced allostery (Du et al., 2022).

Function  
Expression: Enriched in myeloid lineages (neutrophils, monocytes, macrophages, mast cells) and mantle-zone B lymphocytes (Lee et al., 2011; Link & Zutter, 1995).  
Upstream receptors: FcεRI, FcγR and β2/β1 integrins (Lee et al., 2011).  
Downstream signalling: Phosphorylates/activates Syk, LAT, SLP76, Gab2, Akt, ERK1/2, p38 and JNK, promoting mast-cell degranulation and cytokine/leukotriene production (Lee et al., 2011). Constitutive activity supports proliferation and transformation in acute myeloid leukaemia (AML) cells (Shen et al., 2018).  
Cellular roles: Facilitates IgE-mediated anaphylaxis, governs cytoskeletal rearrangement, adhesion and migration in neutrophils/macrophages, and can negatively modulate ITGB2-mediated phagocytosis in selected contexts (Lee et al., 2011).

Inhibitors  
• A-419259: type I, αC-out/DFG-in, stabilises closed conformation (Du et al., 2022).  
• TL02-59: type II, αC-in/DFG-out, displaces SH3 and SH2, creating an open state (Du et al., 2022).

Other Comments  
Over-expression and constitutive activation of Fgr are linked to AML (Shen et al., 2018). Cancer-associated SH3 mutations cluster in RT and distal loops, potentially perturbing regulatory interactions (Pérez et al., 2022). Fgr knock-down reduces passive cutaneous anaphylaxis in mice, highlighting therapeutic potential in allergic disease (Lee et al., 2011).

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