## Phylogeny

Tyrosine-protein kinase Fgr belongs to the Src family of non-receptor tyrosine kinases, a well-conserved group that emerged early in eukaryotic evolution and is present across all metazoans. Within this family, Fgr clusters with the myeloid-enriched members Hck and Lyn and is predominantly expressed in hematopoietic cells such as neutrophils, monocytes, macrophages and mast cells (Hatakeyama et al., 1994; Sen & Johnson, 2011; Fumagalli et al., 2007).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate + H⁺ (Kemble, 2009).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Kemble, 2009).

## Substrate Specificity

Fgr preferentially phosphorylates tyrosine residues located within phosphotyrosine-containing motifs that are recognized through its SH2 domain. Sequential phosphorylation of HS1 (Tyr-222) exemplifies this mechanism, where prior Syk-mediated priming enables efficient Fgr phosphorylation. Although Fgr targets sequences similar to those recognized by other Src kinases, a unique universal consensus motif has not been defined (Brunati et al., 1999).

## Structure

Fgr exhibits the canonical Src-family architecture: an N-terminal myristoylated unique region (membrane targeting), followed by SH3 and SH2 domains, a conserved catalytic (kinase) domain and a short C-terminal regulatory tail. The distinct N-terminal segment and the C-terminal tyrosine involved in negative regulation (via intramolecular SH2 binding) are key features that modulate localization and activity (Hatakeyama et al., 1994; Kemble, 2009).

## Regulation

Activity is governed by multiple phosphorylation events and protein–protein interactions.  
• Activation: autophosphorylation within the kinase domain (Kemble, 2009).  
• Inhibition: phosphorylation of the conserved C-terminal tyrosine by C-terminal Src kinase (Csk) stabilizes an inactive conformation (Ruzzene et al., 1994).  
• Receptor/adapter control: Fc-receptor cross-linking, integrin engagement, and association with adaptor proteins enhance or modulate activity (Hamada et al., 1993; Vines et al., 2001).  
• Pathogenic mutation: the gain-of-function p.Asp502Gly substitution perturbs normal regulatory phosphorylation and promotes autoinflammatory bone disease (Abe et al., 2019).

## Function

Fgr transduces signals from surface receptors that lack intrinsic kinase activity, regulating adhesion, migration, phagocytosis and cytoskeletal remodeling in myeloid cells.  
• Neutrophils: required for fMLP-induced actin reorganization, Rac activation and the respiratory burst (Fumagalli et al., 2007).  
• Monocytes/macrophages: supports ITGB1/ITGB2 signaling for spreading and adhesion but can also attenuate β2-integrin/Syk pathways (Vines et al., 2001).  
• Mast cells: contributes to degranulation and cytokine release through PLD2 phosphorylation (Jing et al., 2021).  
• Additional substrates include CBL, VAV2, PTK2/FAK1 and HCLS1, linking Fgr to survival, proliferation and migration pathways (Fumagalli et al., 2007; Weir et al., 2018).  
Pathological roles include over-expression in subsets of acute myeloid leukemia and involvement in autoinflammatory bone disease (Abe et al., 2019; Weir et al., 2018).

## Inhibitors

The N-phenylbenzamide compound TL02-59 is a picomolar-potent, selective ATP-competitive inhibitor of Fgr that suppresses acute myeloid leukemia cell growth in vitro and in vivo (Weir et al., 2018).

## Other Comments

Selective Fgr inhibition underscores its therapeutic potential in cancer and inflammatory disorders. Integrin and Fc-receptor signaling contexts highlight its central role in immune cell activation and migration (Hamada et al., 1993; Fumagalli et al., 2007).

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