1. Phylogeny  
   Fgr is a member of the Src family of non‐receptor protein tyrosine kinases and, like other family members such as Src, Hck, Lyn, Fyn, Yes, Lck, and Blk, its orthologs are found across mammals and other vertebrates (brickell1991thecsrcfamily pages 1-3). Within the human kinome, Fgr is classified in the Src-related group and shows an evolutionarily conserved domain organization that dates back to early eukaryotic ancestors (korademirnics2000srckinasemediatedsignaling pages 2-3, shen2018thesrcfamily pages 1-2). Its evolutionary history also reveals relationships with primordial Src kinases found in unicellular organisms, underscoring its conserved role in immune-specific signaling pathways (ciapala2017thesrcfamilykinase pages 26-30, shen2018thesrcfamily pages 7-8).
2. Reaction Catalyzed  
   Fgr catalyzes the ATP-dependent phosphorylation of tyrosine residues on protein substrates. The general reaction mechanism is:  
   ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺ (shen2018thesrcfamily pages 1-2, patel1988structureandexpression pages 3-3).
3. Cofactor Requirements  
   The kinase activity of Fgr requires divalent metal ion cofactors, with Mg²⁺ serving as an essential cofactor that facilitates the transfer of the γ-phosphate group from ATP to its substrate (kemble2009abiochemicalstudy pages 18-23, patel1988structureandexpression pages 3-3).
4. Substrate Specificity  
   Fgr phosphorylates tyrosine residues on target proteins that participate in immune and integrin-mediated signaling pathways. Its substrate specificity has been characterized by its ability to phosphorylate proteins such as HS1 in hematopoietic cells, with reports identifying tyrosine 222 of HS1 as a target (brunati1999molecularfeaturesunderlying pages 1-2). In addition, Fgr has been shown to phosphorylate elements of the receptor signaling apparatus, including Syk, PLD2, and components involved in actin cytoskeleton regulation (shen2018thesrcfamily pages 6-6, vines2001inhibitionofβ2 pages 1-2). Although a well-defined consensus substrate motif has not been conclusively established, its activity is largely mediated by recognition of phosphotyrosine sites on substrates involved in immune receptor complex formation (gocek2014nonreceptorproteintyrosine pages 2-3, inoue1991humancfgrinduces pages 5-6).
5. Structure  
   Fgr exhibits the canonical domain composition of Src family kinases. At its extreme N-terminus, it contains a myristoylation signal that mediates plasma membrane association (brickell1991thecsrcfamily pages 1-3, hatakeyama1994themurinecfgr pages 1-2). This is followed sequentially by a unique region that confers additional specificity, an SH3 domain that facilitates interactions with proline-rich sequences, and an SH2 domain that binds phosphotyrosine-containing motifs (shen2018thesrcfamily pages 1-2, giagulli2006thesrcfamily pages 1-1). Next, the catalytic SH1 (kinase) domain is present, which mediates ATP binding and phosphotransfer activity; within this domain lies the activation loop containing the critical autophosphorylation site (Tyr416 in Src numbering) (shen2018thesrcfamily pages 6-6, kemble2009abiochemicalstudy pages 38-43). A unique structural feature of Fgr is found in its activation loop, where a distinct “NPC” (Asn-Pro-Cys) motif replaces the canonical “TAR” sequence seen in other Src family kinases; this alteration appears to correlate with its relatively high basal kinase activity and its capacity to transform cells independently of classical SH3–SH2 mediated autoinhibition (shen2018thesrcfamily pages 7-8, shen2018thesrcfamily pages 3-3). Although no high-resolution crystal structure is currently available specifically for Fgr, homology models based on other Src kinases provide insight into its overall three-dimensional organization, including the positioning of the C-helix, the hydrophobic spine, and the location of key regulatory residues (loris2007exploringstructureand pages 149-152, hatakeyama1994themurinecfgr pages 3-3).
6. Regulation  
   Unlike many other Src family members, Fgr’s kinase activity is manifest in a constitutively active state in certain myeloid cells, as it functions independently of the conventional SH3- and SH2-domain autoinhibitory interactions (shen2018thesrcfamily pages 2-3, shen2018thesrcfamily pages 3-3). Autophosphorylation of the activation loop tyrosine is observed, yet modifications at the C-terminal regulatory tyrosine equivalent do not further enhance its activity in the same way they do for Src or Hck (shen2018thesrcfamily pages 6-6, inoue1991humancfgrinduces pages 1-2). Fgr also undergoes redox-dependent regulation via a conserved cysteine residue located in the glycine loop; oxidation at this site can promote dimerization through disulfide bond formation, a feature conserved among Src, Yes, and Fgr (kemble2009abiochemicalstudy pages 94-100). Additionally, Fgr participates in feedback regulation within immune signaling complexes by interacting with phosphatases such as SHP-1 upon association with ITIM-bearing receptors, thereby modulating downstream substrate phosphorylation including that of Syk (gresham2000negativeregulationof pages 7-8, vines2001inhibitionofβ2 pages 12-13). These regulatory mechanisms underscore a distinct balance between activation and inhibition in Fgr that is context dependent, with differential responses observed in monocytes versus other hematopoietic cells (ciapala2017thesrcfamilykinase pages 90-93).
7. Function  
   Fgr is predominantly expressed in myeloid lineage cells such as neutrophils, monocytes, macrophages, and mast cells. Its expression profile also extends to natural killer cells and certain B-lymphocyte subsets, particularly under conditions of transformation or viral infection (hatakeyama1994themurinecfgr pages 1-2, inoue1991humancfgrinduces pages 1-2). In immune cells, Fgr transmits signals from cell surface receptors that lack intrinsic kinase activity, operating downstream of receptors such as Fc receptors (FCGR2A/FCGR2B), integrins (ITGB1 and ITGB2), and components of the mast cell receptor complex (MS4A2/FCER1B) (shen2018thesrcfamily pages 1-2, ciapala2017thesrcfamilykinase pages 90-93). Through phosphorylation of substrates like Syk, PLD2, and even components of the cytoskeleton such as HCLS1 and cortactin, Fgr modulates key cellular processes including: • Phagocytosis and integrin-mediated cell adhesion and spreading in monocytes and macrophages (vines2001inhibitionofβ2 pages 1-2, vines2001inhibitionofβ2 pages 9-10).  
   • Cytoskeleton remodeling and cell migration through activation of RAC1 and regulation of downstream signaling cascades like the PI3K-AKT and MAP kinase pathways (shen2018thesrcfamily pages 6-6, ciapala2017thesrcfamilykinase pages 26-30).  
   • Mast cell degranulation, which results in the release of inflammatory cytokines and contributes to IgE-mediated anaphylaxis, in part by phosphorylating PLD2 leading to the generation of lipid second messengers such as diacylglycerol and lysophosphatidic acid (shen2018thesrcfamily pages 1-2, ciapala2017thesrcfamilykinase pages 90-93).  
   • Negative regulation of ITGB2-dependent signaling in monocytes by attenuating Syk activity, which is achieved through SH2-mediated binding that inhibits further phosphorylation events (gresham2000negativeregulationof pages 7-8, vines2001inhibitionofβ2 pages 12-13).  
   • Regulation of additional proteins including FASLG, ABL1, CBL, PTK2/FAK1, and VAV2 by direct phosphorylation, thereby influencing their subsequent ubiquitination, internalization, or downstream signaling (shen2018thesrcfamily pages 1-2).
8. Other Comments  
   Fgr is noted for its dual role in cellular signaling: it can act as a positive regulator in contexts that require activation of migration and cytoskeletal reorganization, and as a negative regulator that limits ITGB2-mediated adhesion and phagocytosis in monocytes (shen2018thesrcfamily pages 6-6, vines2001inhibitionofβ2 pages 9-10). This dichotomy makes Fgr a potential therapeutic target in diverse pathological conditions, including acute myeloid leukemia (AML), where its overexpression is associated with oncogenic transformation (shen2018thesrcfamily pages 1-2, inoue1991humancfgrinduces pages 6-6). General Src family kinase inhibitors such as dasatinib may also affect Fgr activity; however, its unique regulatory features suggest that specific inhibitors may be required to effectively modulate its function without off-target effects on other Src kinases (shen2018thesrcfamily pages 2-3, ciapala2017thesrcfamilykinase pages 90-93). No detailed mutational catalog for Fgr has been established in the context provided, and its substrate consensus motifs remain less clearly defined compared to serine/threonine kinases (brunati1999molecularfeaturesunderlying pages 1-2, gocek2014nonreceptorproteintyrosine pages 2-3).
9. References  
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