## Phylogeny

Tyrosine-protein kinase JAK1 is classified within the Tyrosine Kinase (TK) group and the Janus kinase (JAK) family, according to the kinome classification by Manning et al., 2002 (aliceavelazquez2011theuseof pages 2-3, babon2014themolecularregulation pages 4-6, glassman2022structureofa pages 9-11, liu2009combinedinhibitionof pages 1-2, yaronbarir2024theintrinsicsubstrate pages 16-16). The JAK family includes JAK1, JAK2, JAK3, and TYK2 (glassman2022structureofa pages 9-11, wang2003mechanismofjanus pages 1-2). JAK1 shares approximately 23% sequence identity and 48% similarity with other JAK family members (liau2019enzymaticcharacterizationof pages 1-3). Its orthologs are conserved across vertebrates; human JAK1 shares over 90% sequence identity with its mouse and rat orthologs (knoops2011jak1(januskinase pages 1-3), liau2019enzymaticcharacterizationof pages 14-15).

## Reaction Catalyzed

The enzyme catalyzes the transfer of a phosphate group from an ATP substrate to a tyrosine residue on a protein substrate (liau2019enzymaticcharacterizationof pages 15-16). The reaction is represented as: ATP + substrate protein (with tyrosine residues) → ADP + phosphorylated substrate protein (liau2019enzymaticcharacterizationof pages 14-15) or ATP + protein tyrosine → ADP + phosphoprotein tyrosine (liu2009combinedinhibitionof pages 1-2).

## Cofactor Requirements

Catalytic activity requires divalent metal ions, specifically Mg²⁺ or Mn²⁺ (knoops2011jak1(januskinase pages 1-3), knoops2011jak1(januskinase pages 3-3, liau2019enzymaticcharacterizationof pages 14-15). Mg²⁺ is necessary for ATP-dependent phosphorylation, and its chelation disrupts ATP binding (liau2019enzymaticcharacterizationof pages 5-9, liau2019enzymaticcharacterizationof pages 11-14).

## Substrate Specificity

JAK1 preferentially phosphorylates tyrosines within specific sequence contexts (yaronbarir2024theintrinsicsubstrate pages 16-16). According to Yaron-Barir et al., 2024, JAK1 exhibits a preference for acidic residues at the -1 position and for proline or aromatic residues at the +1 position relative to the phosphorylation site (glassman2022structureofa pages 9-11). Another study notes that JAK1 preferentially phosphorylates tyrosines within consensus motifs enriched in acidic residues (liu2009combinedinhibitionof pages 1-2). Known substrates include STAT family proteins (knoops2011jak1(januskinase pages 1-3)).

## Structure

JAK1 is a ~133.3 kDa protein composed of 1154 amino acids, organized into several domains: an N-terminal FERM domain for receptor binding, an SH2 domain, a central pseudokinase domain (JH2) that acts as a negative regulator, and a C-terminal tyrosine kinase domain (JH1) responsible for catalysis (knoops2011jak1(januskinase pages 1-3), babon2014themolecularregulation pages 4-6, liau2019enzymaticcharacterizationof pages 1-3). The kinase domain has a conserved bi-lobed fold and contains a highly conserved ATP-binding site formed by the P-loop, A-loop, hinge region, and DFG motif (aliceavelazquez2011theuseof pages 1-2, wang2023discoveryofnovel pages 1-2). Key residues in the inhibitor binding pocket include Leu1010, Val889, Leu959, Phe958, Leu881, and Arg1007 (sk2022unravelingthemolecular pages 8-9). Crystal structures for the JAK1 kinase domain have been solved (PDB IDs 3EYG and 3EYH), captured in a DFG-out conformation with a phosphorylated activation loop (aliceavelazquez2011theuseof pages 2-3). Structures for the FERM-SH2 and pseudokinase-kinase domains are also available, though no full-length structure has been solved (glassman2022structureofa pages 9-11, liau2019enzymaticcharacterizationof pages 1-3).

## Regulation

JAK1 activity is regulated by phosphorylation, its pseudokinase domain, and interacting proteins. Activation requires trans-autophosphorylation at tyrosines Y1034 and Y1035 within the activation loop, which enhances catalytic activity (knoops2011jak1(januskinase pages 3-3, liu2009combinedinhibitionof pages 1-2, wang2003mechanismofjanus pages 1-2). This phosphorylation is reversible, as the phosphatase PTP1B deactivates JAK1 (liau2019enzymaticcharacterizationof pages 11-14). The pseudokinase (JH2) domain is autoinhibitory, decreasing the turnover rate (kcat) approximately 30-fold while increasing ATP affinity (liau2019enzymaticcharacterizationof pages 9-11, liau2019enzymaticcharacterizationof pages 14-15). Negative regulation is also mediated by Suppressor of Cytokine Signaling (SOCS) proteins, particularly SOCS1 and SOCS3 (aliceavelazquez2011theuseof pages 1-2). SOCS proteins bind to phosphorylated receptors or JAKs, inhibit kinase activity via a pseudosubstrate mechanism, and promote ubiquitination and proteasomal degradation (babon2014themolecularregulation pages 4-6, glassman2022structureofa pages 9-11).

## Function

JAK1 is a ubiquitously expressed, intracellular non-receptor tyrosine kinase that mediates signal transduction for cytokine receptors lacking intrinsic kinase activity (knoops2011jak1(januskinase pages 1-3)). It constitutively associates with the membrane-proximal box1/box2 region of multiple cytokine receptor families, including type I and II interferon, gamma-C (IL-2, IL-4), and gp130 (IL-6, OSM) receptors (radtke2002novelroleof pages 1-1, knoops2011jak1(januskinase pages 1-3, wang2003mechanismofjanus pages 1-2). Upon cytokine binding, JAK1 is activated and phosphorylates tyrosine residues on the receptor, creating docking sites for STAT transcription factors (liau2019enzymaticcharacterizationof pages 1-3). JAK1 then phosphorylates and activates STATs, including STAT1, STAT3, STAT5a, and STAT5b, which translocate to the nucleus to regulate gene expression (liu2009combinedinhibitionof pages 1-2, wang2003mechanismofjanus pages 1-2). Additionally, JAK1 kinase activity promotes the maturation and surface expression of the oncostatin M receptor (OSMR) (radtke2002novelroleof pages 1-1).

## Inhibitors

Small molecule inhibitors targeting the ATP-binding site of JAK1 are used clinically (wang2023discoveryofnovel pages 1-2). They are classified based on their selectivity. Tofacitinib and Ruxolitinib are considered pan-JAK inhibitors that affect multiple family members (aliceavelazquez2011theuseof pages 1-2, glassman2022structureofa pages 9-11). However, some sources describe Ruxolitinib as being primarily selective for JAK1 and JAK2, and Tofacitinib as a JAK1/JAK3 inhibitor (aliceavelazquez2011theuseof pages 2-3, babon2014themolecularregulation pages 4-6, liu2009combinedinhibitionof pages 1-2). Upadacitinib and Filgotinib are classified as JAK1-selective inhibitors, designed to reduce off-target effects (aliceavelazquez2011theuseof pages 1-2, glassman2022structureofa pages 9-11). Other known inhibitors include Itacitinib, which has a reported Ki of 0.5-2 nM, Abrocitinib, and Baricitinib (liau2019enzymaticcharacterizationof pages 9-11, wang2023discoveryofnovel pages 1-2, sk2022unravelingthemolecular pages 8-9).

## Other Comments

Somatic gain-of-function mutations in JAK1 are implicated in hematopoietic and solid tumors, including T-cell acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and breast cancer (knoops2011jak1(januskinase pages 1-3), knoops2011jak1(januskinase pages 3-3)). Activating mutations, such as V658F, A634D, and R724H, are often located in the pseudokinase domain and promote constitutive, cytokine-independent activation of the JAK-STAT pathway (knoops2011jak1(januskinase pages 1-3), babon2014themolecularregulation pages 4-6). The V658F mutation does not alter the intrinsic catalytic parameters (kcat, KM), thermal stability, or inhibitor sensitivity of the isolated enzyme in vitro; its oncogenic effect is attributed to the disruption of cellular autoinhibitory mechanisms within the receptor complex (liau2019enzymaticcharacterizationof pages 1-3, liau2019enzymaticcharacterizationof pages 9-11).

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