## Phylogeny

Tyrosine-protein kinase JAK1 belongs to the Tyrosine Kinase group, Janus kinase (JAK) family, which also includes JAK2, JAK3 and TYK2 (Alicea-Velázquez & Boggon, 2011; Glassman et al., 2022). JAK1 shares ≈23 % sequence identity and 48 % similarity with the other JAK paralogues (Liau et al., 2019). Orthologues are highly conserved in vertebrates; human JAK1 shows >90 % sequence identity with mouse and rat proteins (Knoops et al., 2011; Liau et al., 2019).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine phosphate (Liau et al., 2019; Liu et al., 2009).

## Cofactor Requirements

Catalysis requires divalent metal ions, with Mg²⁺ (preferred) or Mn²⁺ supporting activity; chelation of Mg²⁺ blocks ATP binding (Knoops et al., 2011; Liau et al., 2019).

## Substrate Specificity

JAK1 preferentially phosphorylates tyrosines preceded (–1) by acidic residues and followed (+1) by Pro or aromatic residues (Yaron-Barir et al., 2024; Glassman et al., 2022). Consensus motifs are generally acidic (Liu et al., 2009). Documented cellular substrates include STAT1, STAT3, STAT5a and STAT5b (Knoops et al., 2011).

## Structure

The 1 154-residue (~133 kDa) protein comprises an N-terminal FERM domain, an SH2 domain, a central pseudokinase (JH2) domain and a C-terminal catalytic kinase (JH1) domain (Knoops et al., 2011; Babon et al., 2014). Crystal structures of the isolated kinase domain (PDB 3EYG, 3EYH) show the canonical bilobal fold in a DFG-out conformation with a phosphorylated activation loop (Alicea-Velázquez & Boggon, 2011). Key ATP-site residues include Leu881, Val889, Leu959, Phe958, Leu1010 and Arg1007 (Sk et al., 2022). Structures for the FERM-SH2 and JH2-JH1 tandems are available, but a full-length structure has not yet been reported (Glassman et al., 2022; Liau et al., 2019).

## Regulation

Activity is increased by trans-autophosphorylation of Y1034/Y1035 within the activation loop (Knoops et al., 2011; Wang et al., 2003). The pseudokinase (JH2) domain autoinhibits catalysis, lowering k\_cat ~30-fold and increasing ATP affinity (Liau et al., 2019). Dephosphorylation by PTP1B reverses activation (Liau et al., 2019). Negative regulation is also mediated by SOCS1 and SOCS3, which bind JAK1 or associated receptors and act as pseudosubstrates or E3 adaptors (Alicea-Velázquez & Boggon, 2011; Babon et al., 2014).

## Function

JAK1 is a ubiquitously expressed, non-receptor tyrosine kinase that associates constitutively with the box1/box2 regions of many cytokine receptors, including type I/II interferon, γ\_c-family (IL-2, IL-4) and gp130-family (IL-6, oncostatin M) receptors (Radtke et al., 2002; Knoops et al., 2011). Cytokine binding triggers JAK1 activation, phosphorylation of receptor cytoplasmic tyrosines, recruitment and phosphorylation of STAT1/3/5, and subsequent transcriptional responses (Liau et al., 2019; Liu et al., 2009). JAK1 kinase activity also promotes maturation and surface delivery of the oncostatin M receptor (Radtke et al., 2002).

## Inhibitors

Clinically used ATP-competitive inhibitors include the pan-JAK agents tofacitinib and ruxolitinib (Alicea-Velázquez & Boggon, 2011; Glassman et al., 2022). Ruxolitinib shows preference for JAK1/2, whereas tofacitinib favors JAK1/3 (Babon et al., 2014; Liu et al., 2009). Selective JAK1 inhibitors comprise upadacitinib, filgotinib, itacitinib (K\_i ≈ 0.5–2 nM), abrocitinib and baricitinib (Liau et al., 2019; Wang et al., 2023; Sk et al., 2022).

## Other Comments

Somatic gain-of-function mutations (e.g., V658F, A634D, R724H) in the JH2 domain drive constitutive JAK-STAT signaling in T-cell ALL, AML and some solid tumours (Knoops et al., 2011; Babon et al., 2014). The V658F variant does not change intrinsic catalytic parameters, thermal stability or inhibitor sensitivity in vitro, indicating oncogenicity arises from disrupted autoinhibition in the cellular context (Liau et al., 2019).

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