## Phylogeny

JAK2 is one of four members of the Janus kinase (JAK) subfamily of non-receptor protein tyrosine kinases, together with JAK1, JAK3 and TYK2 (Hubbard, 2018; LaFave & Levine, 2012). Orthologs are conserved across common model organisms, including mouse, rat, chicken, zebrafish and the Drosophila Hop kinase (Sandberg et al., 2007; Lindauer et al., 2001).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + phospho-protein-L-tyrosine (Lindauer et al., 2001; Sandberg et al., 2007; Sanz et al., 2011).

## Cofactor Requirements

Catalytic activity requires divalent cations. JAK2 can use Mg²⁺ or Mn²⁺, with several studies noting a preference for Mn²⁺. The JH2 pseudokinase domain coordinates a single Mg²⁺ via Asn678 and Asp699 (Gabler et al., 2013; Gnanasambandan & Sayeski, 2011; Silvennoinen et al., 2013).

## Substrate Specificity

Peptide profiling shows selectivity at residues –1 to +3 around the phospho-acceptor tyrosine, favouring aliphatic hydrophobic residues at –1 and +3 (Yaron-Barir et al., 2024). JAK2 preferentially phosphorylates motifs containing acidic residues (Asp/Glu) at +1 and +3, a pattern present in STAT proteins and many cytokine-receptor tails (Sanz et al., 2011). Kinase-wide clustering places JAK2 in a distinct JAK family group (Yaron-Barir et al., 2024).

## Structure

The protein contains seven Janus homology (JH) regions (JH7–JH1):

• FERM domain (JH7-JH5) – cytokine-receptor binding  
• SH2-like domain (JH4-JH3) – structural support for receptor interaction  
• Pseudokinase domain (JH2) – autoinhibitory regulator; HRD → HGN variation in catalytic loop  
• Kinase domain (JH1) – catalytic core (Dusa et al., 2010; Hubbard, 2018; Silvennoinen et al., 2013)

Homology modelling against insulin receptor and FGFR kinases indicates a canonical bilobal tyrosine-kinase fold with an activation loop, catalytic loop, nucleotide-binding loop and αC-helix (Lindauer et al., 2001). The pathogenic V617F mutation in JH2 rigidifies the αC-helix through π-stacking with Phe594/Phe595, promoting constitutive activation (Silvennoinen et al., 2013).

## Regulation

• Autoinhibition: JH2 suppresses JH1 in the basal state (Dusa et al., 2010; Hubbard, 2018).  
• Activation: Ligand-induced receptor dimerisation triggers trans-phosphorylation of Y1007/Y1008 in the JH1 activation loop (Dusa et al., 2010; Gabler et al., 2013).  
• Intramolecular phosphorylation: JH2 autophosphorylation at Ser523 and Tyr570 modulates activity; Ser523 is inhibitory (Silvennoinen et al., 2013; Sanz et al., 2011).  
• Deactivation: SHP1, CD45 and SOCS proteins de-phosphorylate or target JAK2 for degradation (Gnanasambandan & Sayeski, 2011; Santos & Verstovsek, 2011).

## Function

Ubiquitously expressed, JAK2 couples cytokine receptors lacking intrinsic kinase activity to intracellular signalling (Sandberg et al., 2007; Santos & Verstovsek, 2011).

Upstream: associates with receptors such as EPOR, TPOR and interferon receptors (Dusa et al., 2010; Hubbard, 2018).

Downstream: phosphorylates STAT3 and STAT5, which dimerise and translocate to the nucleus; JAK2 also interfaces with MAPK and PI3K pathways (Santos & Verstovsek, 2011).

Biological roles: indispensable for definitive erythropoiesis, myeloid and megakaryocytic development (Santos & Verstovsek, 2011). Nuclear JAK2 can phosphorylate histone H3 at Tyr41, influencing chromatin state (LaFave & Levine, 2012).

## Inhibitors

Clinically approved ATP-competitive inhibitors include ruxolitinib, fedratinib and pacritinib (Nair et al., 2023; Vainchenker et al., 2018). Experimental inhibitors such as TG101348 and Z3 have been characterised (Dusa et al., 2010; Sayyah & Sayeski, 2009). Allosteric strategies targeting the kinase–pseudokinase interface are under exploration (Gnanasambandan & Sayeski, 2011).

## Other Comments

Gain-of-function mutations drive myeloproliferative neoplasms, most notably V617F in >95 % of polycythaemia vera and ~50 % of essential thrombocythaemia and primary myelofibrosis cases (Silvennoinen et al., 2013). Additional activating mutations occur in the SH2-JH2 linker, and translocations such as TEL-JAK2 generate constitutively active fusion kinases (Gnanasambandan & Sayeski, 2011; Janus kinases in immune cell signaling, 2009).

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