## Phylogeny

Tyrosine-protein kinase JAK2 is one of four Janus kinases (JAK1, JAK2, JAK3, TYK2). Orthologues are found from early metazoans to mammals, and the typical JAK domain architecture—N-terminal FERM and SH2-like modules followed by a regulatory pseudokinase domain (JH2) and a C-terminal catalytic kinase domain (JH1)—is conserved across vertebrates (Babon et al., 2014; Karjalainen, 2016; Mingione et al., 2023). JAK2 transcripts are detected in most mammalian tissues, consistent with its broad role in cytokine signalling (Kwon, 2022).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺ (Matsuda et al., 2004).

## Cofactor Requirements

Catalysis requires a divalent metal ion, predominantly Mg²⁺; Mn²⁺ can substitute in vitro (Endicott et al., 2012; Matsuda et al., 2004).

## Substrate Specificity

JAK2 phosphorylates tyrosine residues in the cytoplasmic tails of type I/II cytokine receptors and on STAT transcription factors. Peptide-array studies indicate sequence context around the target Tyr influences efficiency, although no single consensus motif is universal (Sanz et al., 2011; Deng et al., 2014). Additional cellular substrates include CDKN1B, histone H3 (Tyr41), and ARHGEF1 (Hammarén et al., 2015; Deng et al., 2014).

## Structure

JAK2 is a multidomain protein:  
• FERM domain (membrane/receptor binding)  
• SH2-like domain (stabilises receptor interaction)  
• Pseudokinase domain JH2 (binds ATP weakly; autoinhibits JH1)  
• Catalytic kinase domain JH1 (bilobal fold with conserved VAIK Lys, C-helix, DFG motif and activation loop)

Tight JH2–JH1 and SH2–JH2 linker interactions modulate ATP affinity and allosteric regulation (Hubbard, 2018; Mingione et al., 2023; Kwon, 2022).

## Regulation

1. Autophosphorylation of Tyr1007 in the JH1 activation loop relieves autoinhibition (Babon et al., 2014; Matsuda et al., 2004).
2. Intramolecular repression: JH2 interacts with JH1 to maintain low basal activity; mutations such as V617F disrupt this clamp and produce constitutive signalling (Hubbard, 2018; Barua et al., 2009).
3. Additional phosphorylation, ubiquitination and dephosphorylation events fine-tune activity and receptor association (Babon et al., 2014; Mingione et al., 2023).

## Function

Upon cytokine binding to receptors (e.g., EPOR, GHR, PRLR, LEPR, MPL), receptor-bound JAK2 molecules trans-activate, phosphorylate receptor tyrosines, recruit STATs, and drive STAT dimerisation and nuclear gene regulation controlling haematopoiesis, immunity, proliferation and survival (Babon et al., 2014; Matsuda et al., 2004). JAK2 also:  
• Links cytokine signals to cell-cycle control via CDKN1B phosphorylation (Deng et al., 2014).  
• Modifies chromatin by phosphorylating histone H3 Tyr41, blocking CBX5 binding (Hammarén et al., 2015).  
• Contributes to vascular stress responses through ARHGEF1 phosphorylation and modulates KCNA3 channel expression (Deng et al., 2014).  
Its ubiquitous expression underscores its central role in multiple signalling pathways (Kwon, 2022).

## Inhibitors

Clinically approved ATP-competitive inhibitors such as ruxolitinib target the JH1 ATP-binding site for treatment of myeloproliferative neoplasms. Second-generation compounds aimed at allosteric or interdomain sites (e.g., within JH2 or the SH2-JH2 linker) are under development to improve specificity and reduce adverse effects (Kwon, 2022; Mingione et al., 2023).

## Other Comments

The disease-linked V617F mutation in JH2 abolishes autoinhibition and is a molecular hallmark of polycythaemia vera, essential thrombocythaemia and primary myelofibrosis (Barua et al., 2009; Hubbard, 2018). Combination therapeutic strategies targeting multiple nodes in the JAK2 network are being explored (Mingione et al., 2023).

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