## Phylogeny

Tyrosine-protein kinase JAK3 is one of four Janus kinases (JAK1, JAK2, JAK3, TYK2) within the non-receptor tyrosine kinase branch. Orthologues occur throughout vertebrates and the enzyme is particularly conserved in hematopoietic lineages of mammals, reflecting its specialized immune function (O’Shea, 2009; Rane & Reddy, 2000). Catalytic regions are highly conserved across the family, whereas regulatory domains have diverged to support lineage-specific roles (Notarangelo et al., 2001; O’Shea, 2009).

## Reaction Catalyzed

ATP + [protein]-tyrosine ⇌ ADP + H⁺ + [protein]-phosphotyrosine (Casimiro-Garcia et al., 2018).

## Cofactor Requirements

Mg²⁺ is required for nucleotide binding and phosphoryl transfer (O’Shea, 2009; Ungureanu, 2005).

## Substrate Specificity

JAK3 phosphorylates tyrosine residues on the cytoplasmic tails of type I cytokine receptors that contain the common γ-chain, notably IL-2Rβ and IL-2Rγ. These phosphotyrosines recruit and are subsequently phosphorylated STAT transcription factors. Specific recognition is mediated by structural features in the kinase domain that engage the receptor motif (Casimiro-Garcia et al., 2018; O’Shea, 2009; Forster et al., 2016).

## Structure

The protein comprises seven Janus homology (JH) segments:  
• FERM domain (JH5-JH7) – binds receptor intracellular regions.  
• SH2-like domain (JH3-JH4) – contributes to receptor interaction.  
• Pseudokinase domain (JH2) – catalytically inactive, modulates JH1.  
• Kinase domain (JH1) – canonical bilobed fold; activation loop contains Y980/Y981 whose phosphorylation activates the enzyme. Conserved DFG and gatekeeper motifs are present. A unique Cys909 in the ATP pocket provides a handle for covalent inhibitors (Casimiro-Garcia et al., 2018; Forster et al., 2017; Wilks, 2008; Vihinen et al., 2000).

## Regulation

Activation requires autophosphorylation of Y980/Y981, while the JH2 pseudokinase exerts basal inhibition (Smith et al., 2016; Vihinen et al., 2000). Negative regulators include SOCS proteins, which recruit ubiquitin machinery, and the tyrosine phosphatases SHP-1 and CD45 that dephosphorylate active JAK3 (Rane & Reddy, 2000; O’Shea, 2009).

## Function

Upon cytokine binding, γ-chain–containing receptors dimerize, juxtaposing JAK3 (often paired with JAK1) and enabling receptor phosphorylation. The resulting STAT docking and phosphorylation cascade drives transcriptional programs essential for T-cell and natural killer cell development, proliferation, and differentiation. JAK3 expression is largely restricted to hematopoietic cells, underpinning its pivotal role in adaptive and innate immunity (Casimiro-Garcia et al., 2018; Notarangelo et al., 2001; Ndiaye et al., 2016; O’Shea, 2009).

## Inhibitors

Selective inhibition exploits Cys909:  
• Tofacitinib (CP-690,550) – first-generation inhibitor.  
• Cyanamide-based, covalent inhibitors (Casimiro-Garcia et al., 2018).  
• Covalent-reversible chemotypes targeting an induced-fit pocket (Forster et al., 2016).  
• Orally available irreversible agents with high isoform selectivity (Shi et al., 2019).  
These compounds serve as probes of JAK3 function and as therapeutics for autoimmune disease and transplant rejection (Forster et al., 2017; Wilks, 2008).

## Other Comments

Loss-of-function mutations in JAK3, particularly within the kinase or FERM domains, cause autosomal-recessive severe combined immunodeficiency (SCID) (Notarangelo et al., 2001).

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