Protein: Tyrosine-protein kinase JAK3 (UniProt P52333)

## Phylogeny

• Kinome placement: Tyrosine Kinase (TK) group, Janus kinase (JAK) family together with paralogues JAK1, JAK2 and TYK2 (yamaoka2004thejanuskinases pages 1-2).  
• Vertebrate orthologs: Homo sapiens JAK3; Mus musculus Jak3 on chromosome 8 (yamaoka2004thejanuskinases pages 1-2); Gallus gallus Jak3 ortholog; Danio rerio jak3 ortholog (yamaoka2004thejanuskinases pages 1-2).  
• Invertebrate ortholog: Drosophila melanogaster Hopscotch, the single ancestral JAK (yamaoka2004thejanuskinases pages 1-2).  
• Evolution: the four-member vertebrate JAK set arose by gene duplication after divergence from the single invertebrate Hopscotch ancestor (yamaoka2004thejanuskinases pages 1-2).

## Reaction Catalyzed

MgATP + protein-L-tyrosine-OH → protein-L-tyrosine-OPO₃²⁻ + MgADP + H⁺ (roskoski2016januskinase(jak) pages 1-8).

## Cofactor Requirements

Catalytic phosphotransfer strictly requires Mg²⁺ as divalent cofactor (roskoski2016januskinase(jak) pages 1-8).

## Substrate Specificity

• Cellular substrates: tyrosine residues within γc-containing cytokine receptor tails and STAT1-6 transcription factors (roskoski2016januskinase(jak) pages 8-12, cetkoviccvrlje2004therapeuticpotentialof pages 1-2).  
• Linear consensus motif: not defined; substrate choice is governed by spatial proximity in cytokine receptor complexes rather than a strict primary-sequence preference (roskoski2016januskinase(jak) pages 8-12).

## Structure

Domain architecture  
1. FERM (JH7-JH6) – receptor binding (yamaoka2004thejanuskinases pages 2-3).  
2. SH2-like (JH5-JH3) – stabilises FERM-receptor interaction (yamaoka2004thejanuskinases pages 2-3).  
3. Pseudokinase JH2 – autoinhibitory regulator (lupardus2014structureofthe pages 6-6).  
4. Catalytic kinase JH1 – executes tyrosyl phosphorylation (yamaoka2004thejanuskinases pages 2-3).

Three-dimensional information  
• Kinase-domain crystal structure PDB 3LXK defines the bilobal fold and ATP pocket (roskoski2016januskinase(jak) pages 58-72).  
• Covalent inhibitor complex PDB 4Z16 shows electrophile attachment to hinge Cys909 unique to JAK3 (tan2015developmentofselective pages 1-3).  
• Catalytic motifs: Gly-rich 829GKGNFG834, β3 Lys855, αC Glu871, HRD Asp949, DFG Asp967, activation segment 967-997 (roskoski2016januskinase(jak) pages 72-78).  
• Regulatory spine anchor Tyr913 and complete catalytic spine align with active kinase architecture (roskoski2016januskinase(jak) pages 78-87).  
• Selectivity residues near ATP site: Ser826, Asn832, Tyr904, Ser907, Cys909 distinguish JAK3 from other JAKs (roskoski2016januskinase(jak) pages 87-87).

## Regulation

Post-translational modifications  
• Activation-loop autophosphorylation enhances catalytic efficiency (babon2014themolecularregulation pages 1-3).  
• Tyr785 phosphorylation recruits SH2-Bβ and augments activity (yamaoka2004thejanuskinases pages 3-4).  
• Tyr841 phosphorylation correlates with oncogenic activation (unknownauthors2016arequirementfor pages 22-27).  
• SOCS1 binding to phosphorylated activation loop promotes poly-ubiquitination via elongin B/C-Cullin-5-Rbx1 E3 ligase, leading to degradation (unknownauthors2008therapeutictargetingof pages 1-2).  
• Tyrosine phosphatases SHP1, SHP2, PTP1B, TCPTP and CD45 dephosphorylate and attenuate signalling (roskoski2016januskinase(jak) pages 8-12).

Allosteric/conformational control  
• Intramolecular JH2-JH1 contacts maintain autoinhibition; cytokine-induced receptor dimerisation or gain-of-function mutations (M511I, A572V, R657Q) disrupt this interface and allow constitutive signalling (lupardus2014structureofthe pages 6-6, raivola2018hyperactivationofoncogenic pages 4-7).

## Function

Expression  
High constitutive expression in NK cells, thymocytes, mast cells and platelets; inducible in activated T and B lymphocytes; minimal in non-hematopoietic tissues (cetkoviccvrlje2004therapeuticpotentialof pages 1-2).

Signalling network  
• Upstream activators: interleukin receptors sharing the γc chain (IL-2, ‑4, ‑7, ‑9, ‑15, ‑21) (cetkoviccvrlje2004therapeuticpotentialof pages 1-2, roskoski2016januskinase(jak) pages 72-78).  
• Obligatory partner kinase: JAK1 forms heterodimers on these receptors (tan2015developmentofselective pages 1-3).  
• Direct substrates: STAT3, STAT5, STAT6 which dimerise and drive transcription of genes governing lymphoid proliferation and differentiation (roskoski2016januskinase(jak) pages 72-78).  
• Adapter/regulators: SH2-Bβ (positive), APS (negative), and STAM/AMSH/HRS endosomal proteins modulate output (unknownauthors2008therapeutictargetingof pages 2-4).

## Inhibitors

ATP-competitive  
• Tofacitinib (CP-690,550) IC₅₀ ≈ 1.6 nM; approved immunomodulator (roskoski2016januskinase(jak) pages 78-87, yamaoka2004thejanuskinases pages 4-5).  
• Decernotinib (VX-509) IC₅₀ ≈ 2 nM; selective JAK3 inhibitor (roskoski2016januskinase(jak) pages 78-87).

Covalent  
• Cyanamide-based electrophiles targeting Cys909 with high selectivity (casimirogarcia2018identificationofcyanamidebased pages 32-33).  
• 4-Aminopyrimidine covalent series exploiting Cys909 (tan2015developmentofselective pages 1-3).

Tool compounds  
• Staurosporine analogues define ATP-pocket geometry but lack selectivity (lupardus2014structureofthe pages 6-6).

## Other Comments

Disease associations  
• Autosomal recessive severe combined immunodeficiency (T- B⁺ NK⁻) caused by loss-of-function JAK3 mutations across all domains (babon2014themolecularregulation pages 4-6, yamaoka2004thejanuskinases pages 3-4).  
• Somatic gain-of-function mutations M511I, A572V, R657Q, L857Q drive T-cell acute lymphoblastic leukaemia and other haematologic malignancies (raivola2018hyperactivationofoncogenic pages 4-7, unknownauthors2008therapeutictargetingof pages 5-6, unknownauthors2016arequirementfor pages 22-27).  
• Additional activating mutations reported in Down-syndrome-associated acute megakaryoblastic leukaemia and myeloproliferative disorders (unknownauthors2008therapeutictargetingof pages 5-6).

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