## Phylogeny

• Member of the protein-tyrosine kinase (TK) group, Janus kinase (JAK) family, clustering with JAK1, JAK2 and JAK3 (borcherding2021tyk2incancer pages 5-6, woss2019tyk2anupstream pages 1-3).  
• Orthologs documented in human (TYK2), mouse (Tyk2), chicken (TYK2) and zebrafish (tyk2), illustrating strong conservation of the four-domain JAK architecture across vertebrates (borcherding2021tyk2incancer pages 5-6).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-O-phosphate (woss2019tyk2anupstream pages 1-3, borcherding2021tyk2incancer pages 5-6).

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that coordinate ATP in the JH1 active site (wang2025atripleactioninhibitory pages 24-32).

## Substrate Specificity

• Cellular substrates include STAT1, STAT3, STAT4, STAT5A/B and receptor tyrosines within IFNAR1, IL-12Rβ1, IL-10Rβ and IL-13Rα1 (borcherding2021tyk2incancer pages 5-6).  
• Recognition is driven by SH2-mediated docking to receptor pY-X-X-L/I motifs; no stringent linear consensus for free peptides has been defined (wang2025atripleactioninhibitory pages 5-8).

## Structure

• Domain organization: N-terminal FERM (JH7-JH5) for receptor binding; SH2-like JH4; JH2 pseudokinase providing autoinhibition/allosteric control; C-terminal JH1 catalytic kinase (borcherding2021tyk2incancer pages 5-6, min2015structuralandfunctional pages 1-2).  
• Isolated JH2 crystal structure (PDB 4OLI, 1.9 Å) adopts a closed active-like fold with a rigid αAL helix replacing the P+1 loop, blocking substrate access and explaining absent phosphotransferase activity (min2015structuralandfunctional pages 6-7).  
• Tandem JH2-JH1 structure reveals extensive N-lobe contacts that lock JH1 in an autoinhibited conformation; interface-disrupting mutations yield constitutive activity (lupardus2014structureofthe pages 5-6).  
• Catalytic landmarks in JH1: Lys930 (VAVK), Glu927 (αC), Asp1010 (HRD), Asp1028 (DFG), gatekeeper Thr981, activation-loop Tyr1054/Tyr1055 that undergo trans-autophosphorylation, and a hydrophobic spine whose alignment accompanies activation (borcherding2021tyk2incancer pages 5-6, min2015structuralandfunctional pages 7-8, wang2025atripleactioninhibitory pages 24-32).

## Regulation

Post-translational modifications  
• Autophosphorylation at Tyr1054/Tyr1055 is essential for full catalytic activity (borcherding2021tyk2incancer pages 5-6).  
• Additional phosphorylation at Ser491/Ser499 modulates signaling amplitude (borcherding2021tyk2incancer pages 5-6).  
• Dephosphorylation by PTP1B and SHP1 attenuates kinase activity (borcherding2021tyk2incancer pages 5-6).  
• SOCS1/3 and the E3 ligase SIAH2 promote ubiquitin-dependent proteasomal degradation (borcherding2021tyk2incancer pages 5-6, woss2019tyk2anupstream pages 6-8).  
• HSP90 acts as a chaperone; its inhibition destabilises TYK2 (borcherding2021tyk2incancer pages 6-8).

Allosteric and conformational control  
• ATP binding to the JH2 pseudokinase thermally stabilises the domain and restricts JH1 flexibility without measurable phosphotransferase activity (min2015structuralandfunctional pages 1-2).  
• Gain-of-function mutations V678F, P760L and G761V in JH2 weaken the JH2-JH1 interface, producing ligand-independent kinase activity (min2015structuralandfunctional pages 7-8, woss2019tyk2anupstream pages 3-5).

## Function

• Broad expression with highest levels in hematopoietic and epithelial cells; indispensable for innate and adaptive immunity, antiviral defence and epithelial homeostasis (woss2019tyk2anupstream pages 1-3, borcherding2021tyk2incancer pages 6-8).  
• Associates with IFNAR1, IL-12Rβ1, IL-10Rβ and IL-13Rα1; complementary receptor chains recruit JAK1 or JAK2 to form functional heterodimers (borcherding2021tyk2incancer pages 5-6).  
• Upon cytokine binding, TYK2 phosphorylates receptor tails and STAT1/3/4/6, driving transcriptional programs governing inflammation, cell survival and differentiation (woss2019tyk2anupstream pages 1-3).  
• Kinase-independent scaffolding by TYK2 is required for surface expression of IFNAR1 and IL-10R2 (sohn2013arestrictedrole pages 2-3).

## Inhibitors

• Deucravacitinib (BMS-986165): high-affinity JH2 allosteric binder that locks TYK2 in the autoinhibited state and suppresses type I IFN and IL-23 signaling in humans (burke2019autoimmunepathwaysin pages 11-12).  
• BMS-986202 and TAK-279: investigational JH2-selective inhibitors exploiting the same pocket (wang2025atripleactioninhibitory pages 5-8).  
• Pyrazine-based ATP-competitive probe for JH2 (Kd ≈ 0.25 µM) enables structural interrogation (min2015structuralandfunctional pages 6-7).  
• Pan-JAK active-site inhibitors such as tofacitinib, baricitinib and ruxolitinib also inhibit TYK2 but lack selectivity (sohn2013arestrictedrole pages 1-2, borcherding2021tyk2incancer pages 8-10).

## Other Comments

• Loss-of-function variants: rs34536443 (P1104A) and splice variant E971fsX67 impair STAT activation, causing immunodeficiency yet confer protection from several autoimmune diseases (borcherding2021tyk2incancer pages 5-6).  
• Gain-of-function variants: V678F, P760L and G761V relieve autoinhibition and are linked to hematologic malignancies (min2015structuralandfunctional pages 7-8, woss2019tyk2anupstream pages 3-5).  
• Oncogenic fusions NPM1-TYK2, NFκB2-TYK2 and MYB-TYK2 create constitutively active kinases driving leukemias and lymphomas (borcherding2021tyk2incancer pages 3-5, woss2019tyk2anupstream pages 5-6).

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