## Phylogeny

Tyrosine-protein kinase TYK2 is one of four Janus kinases (JAK1, JAK2, JAK3, TYK2) that arose from ancient gene-duplication events in early metazoan evolution (Min et al., 2015; Li, 2017). Orthologues are present throughout vertebrates and the TYK2 sequence retains the canonical JAK module of N-terminal FERM, SH2-like, pseudokinase (JH2) and catalytically active kinase (JH1) domains (Min et al., 2015; Eshaq et al., 2024). High sequence identity across the regulatory and catalytic regions, together with its broad but immune-cell-enriched expression pattern, indicates strong evolutionary pressure to preserve TYK2-dependent cytokine signalling (Li, 2017; Borcherding et al., 2021).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺ (Li, 2017; Creeden et al., 2020).

## Cofactor Requirements

Mg²⁺ is required to coordinate ATP in the active site (Min et al., 2015; Eshaq et al., 2024).

## Substrate Specificity

Substrate selection is dictated mainly by the cytokine-receptor complex that recruits TYK2 rather than by a strict peptide consensus. TYK2 phosphorylates tyrosines on the cytoplasmic tails of receptor subunits (e.g., IFNAR1, IL12RB1, IL10RB, IL13RA1) and on downstream STAT proteins (STAT1, STAT3, STAT4, STAT6), generating docking sites that drive STAT dimerisation and nuclear translocation (Li, 2017; Creeden et al., 2020; Eshaq et al., 2024).

## Structure

TYK2 is a multidomain kinase with:  
• FERM domain (membrane-proximal receptor binding).  
• SH2-like domain (additional receptor/partner contacts).  
• Pseudokinase JH2 domain that binds ATP in a non-canonical manner and autoinhibits JH1.  
• C-terminal JH1 kinase domain with the typical bilobal fold, Gly-rich loop, C-helix, activation loop and hydrophobic regulatory spine (Wallweber et al., 2014; Min et al., 2015; Mingione et al., 2023; Wang et al., 2025).  
Crystal structures and AlphaFold models show that, in the basal state, JH2 restrains JH1; receptor engagement relieves this constraint, enabling activation-loop phosphorylation and full catalytic activity (Niranjan, 2014; Wang et al., 2025).

## Regulation

1. Autoinhibition: the JH2 domain locks JH1 in an inactive conformation (Niranjan, 2014).
2. Activation-loop phosphorylation of JH1 reorients the loop and C-helix to align catalytic residues (Niranjan, 2014; Wang et al., 2025).
3. Trans-phosphorylation: within receptor dimers TYK2 phosphorylates receptor chains and STATs, often cooperating with JAK1 or JAK2 (Borcherding et al., 2021; Creeden et al., 2020).
4. Additional control: TYK2 can phosphorylate an inhibitory tyrosine on STAT3, dampening STAT3 activity (Eshaq et al., 2024; Sohn et al., 2013).

## Function

TYK2 is an essential mediator of type I interferon and multiple interleukin (IL-12, IL-10, IL-13) pathways. Upon cytokine binding, TYK2-associated receptor chains dimerise with partners bound by JAK1/JAK2, triggering TYK2 activation, receptor phosphorylation and STAT recruitment. Activated STAT dimers drive gene programmes that coordinate innate and adaptive immunity, cell proliferation and differentiation (Borcherding et al., 2021; Muromoto et al., 2021). TYK2 is highly expressed in immune cells and its dysregulation contributes to autoimmune and inflammatory diseases (Borcherding et al., 2021).

## Inhibitors

Selective allosteric inhibitors that bind the JH2 pseudokinase domain (e.g., deucravacitinib, PF-06826647) stabilise the autoinhibited state and attenuate pathological cytokine signalling with reduced off-target JAK activity (Wang et al., 2025; Gerstenberger et al., 2020; Rusiñol & Puig, 2023).

## Other Comments

Genetic TYK2 variants modulate cytokine responsiveness and disease susceptibility; TYK2 also serves a structural role in maintaining cytokine-receptor surface expression (Borcherding et al., 2021; Sohn et al., 2013). Ongoing clinical trials targeting TYK2 aim to balance efficacy and safety in psoriasis, inflammatory bowel disease and related disorders (Chen et al., 2023; Hromadová et al., 2021).

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