

Exploring the JAK-STAT Pathway

JAK-STAT: What's That?

Janus **K**inase **S**ignal **T**ransducer and **A**ctivator of **T**ranscription (JAK-STAT) pathway

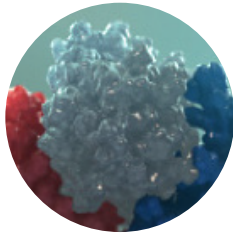
The immune system contains a complex network of cells that fight infectious diseases and respond to cell damage via different signaling pathways

Many pro-inflammatory cytokines involved in the pathogenesis of immune-mediated and inflammatory diseases signal through the JAK-STAT pathway^{1,2}

JAK-STAT Pathway: Key Components

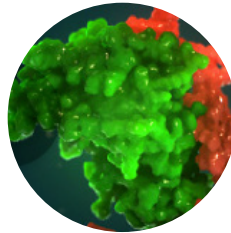
The JAK-STAT pathway includes several key components:

Class I and II cytokines



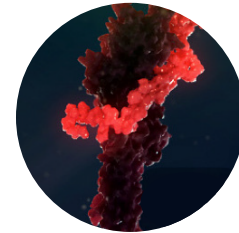
Group of 50+ messenger proteins reliant on JAK and STAT for immune signaling³

JAK enzymes



Four types including JAK1, JAK2, JAK3, TYK2²

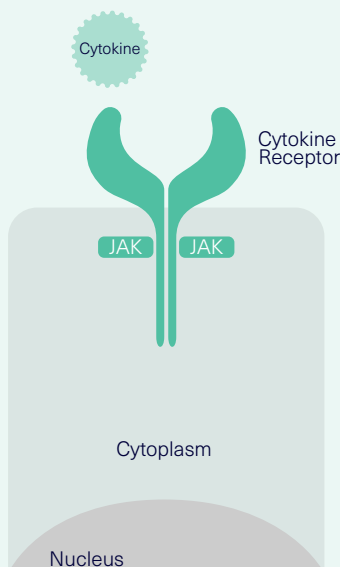
STAT proteins



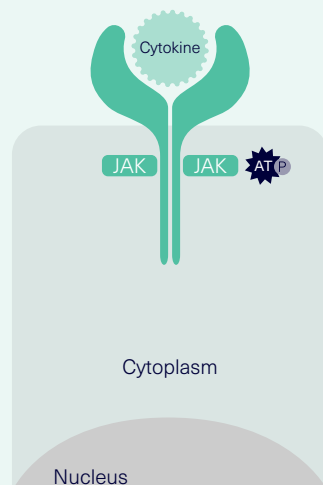
Seven types including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6²

Steps of JAK-STAT Signaling

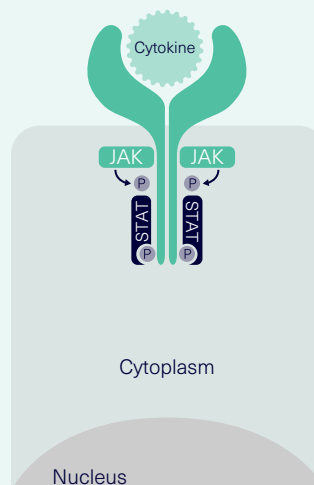
1 JAK-STAT signaling begins with cytokines binding to cell-surface receptors^{4,5}



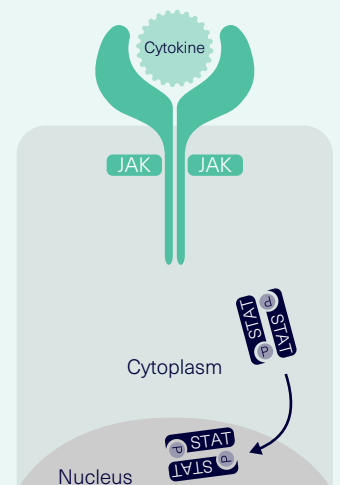
2 After cytokine binding, specific JAK enzymes dimerize and become activated by binding ATP.^{4,5} Activated JAKs add a phosphate molecule to cell-surface receptors, which creates a binding site for STAT proteins^{4,5}



3 STAT proteins become activated by JAKs through the addition of another phosphate molecule^{4,5}



4 Once activated, STAT proteins detach from the receptor, dimerize and travel to the cell nucleus to bind DNA and help regulate the expression of pro-inflammatory genes^{4,5}

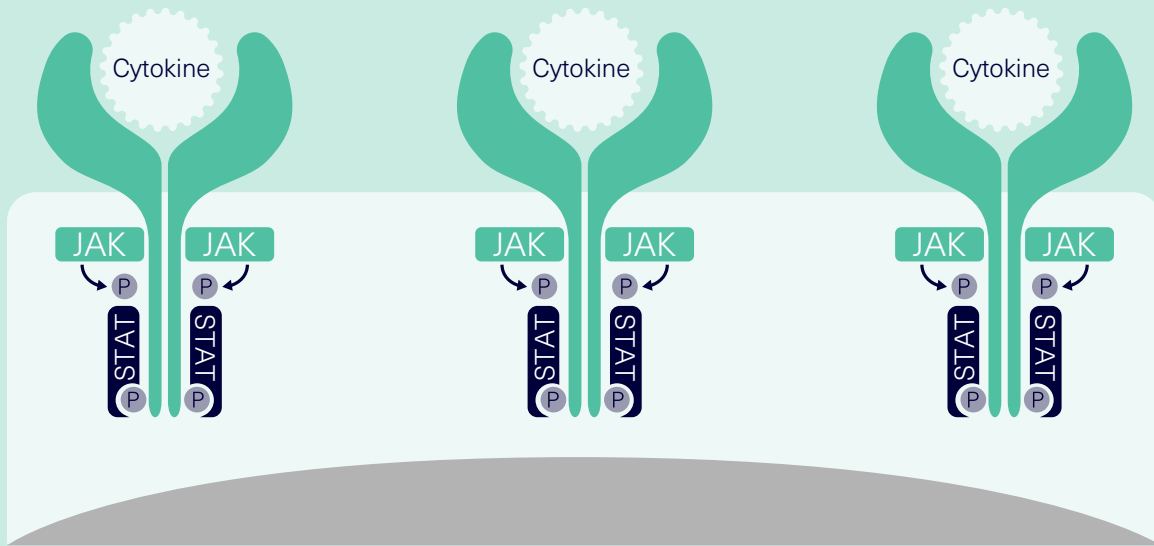


An Altered JAK-STAT Pathway

Altered JAK-STAT signaling can lead to the **development of certain immune-mediated diseases** such as rheumatoid arthritis, psoriasis and inflammatory bowel disease^{2,5}

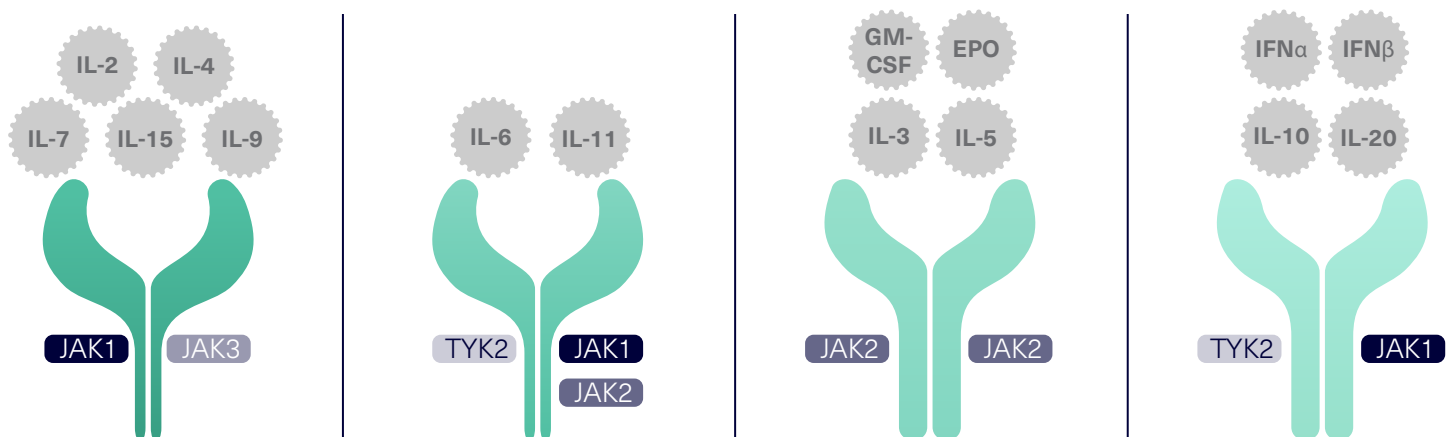
Overexpression of pro-inflammatory cytokines that activate JAK enzymes can lead to increased activation of the JAK-STAT pathway^{2,5}

This increase in pro-inflammatory signaling disrupts the balance required for normal immune responses^{2,5}



Recruiting JAKs to Mediate Cell Signaling

The binding of cytokines to cell-surface receptors initiates recruitment of different combinations of JAK dimers for immune signaling.³ For example, JAK1 is recruited by pro-inflammatory cytokines that are drivers of inflammatory and immune-mediated diseases, including IL-6, the IL-10 family (IL-10, IL-20, IL-22) and type 1 interferons (IFN α / β)³



*Representation of common cytokine and receptor pairings in JAK-STAT signaling. Interleukins (IL), Interferons (IFN), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Hormones [Erythropoietin (EPO)].

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2. Banerjee, Shubhasree, et al. "JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects." *Drugs* 77.5 (2017): 521-546.
3. Schwartz, Daniella M., et al. "JAK inhibition as a therapeutic strategy for immune and inflammatory diseases." *Nature Reviews Drug Discovery* 16.12 (2017): 843.
4. Rawlings, Jason S., Kristin M. Rosler, and Douglas A. Harrison. "The JAK/STAT signaling pathway." *Journal of Cell Science* 117.8 (2004): 1281-1283.
5. O'Shea, John J., et al. "The JAK-STAT pathway: impact on human disease and therapeutic intervention." *Annual Review of Medicine* 66 (2015): 311-328.

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