

# Exploring the JAK-STAT Pathway

## JAK-STAT: What's That?

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

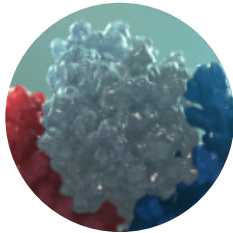
The immune system contains a complex network of cells that fight infectious diseases and respond to cell damage via different signaling pathways

Many pro-inflammatory cytokines involved in the pathogenesis of immune-mediated and inflammatory diseases signal through the JAK-STAT pathway<sup>1,2</sup>

## JAK-STAT Pathway: Key Components

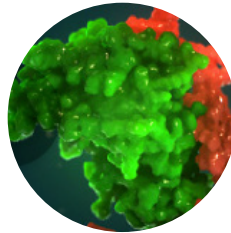
The JAK-STAT pathway includes several key components:

### Class I and II cytokines



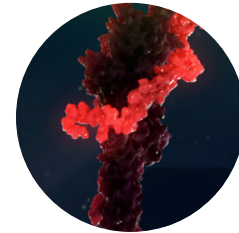
Group of 50+ messenger proteins reliant on JAK and STAT for immune signaling<sup>3</sup>

### JAK enzymes



Four types including JAK1, JAK2, JAK3, TYK2<sup>2</sup>

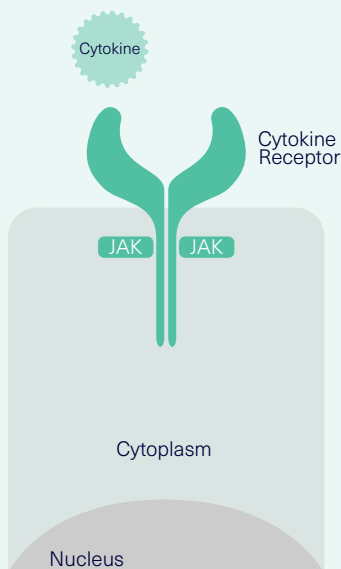
### STAT proteins



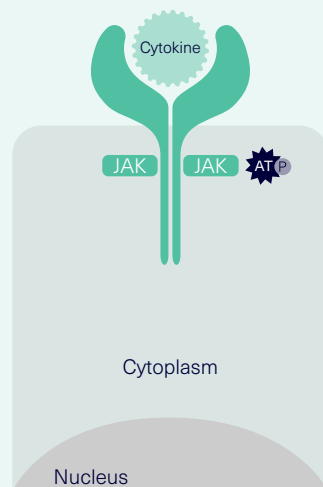
Seven types including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6<sup>2</sup>

## Steps of JAK-STAT Signaling

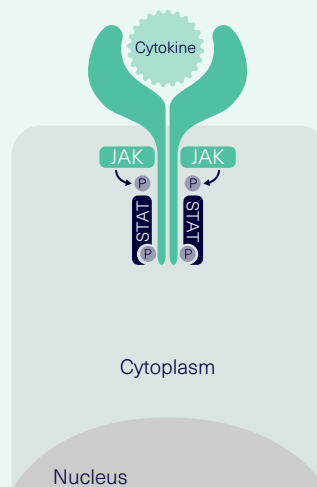
**1** JAK-STAT signaling begins with cytokines binding to cell-surface receptors<sup>4,5</sup>



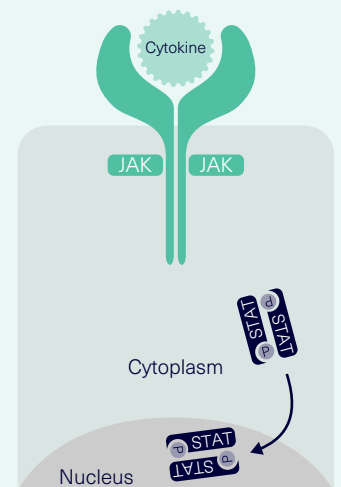
**2** After cytokine binding, specific JAK enzymes dimerise and become activated by binding ATP<sup>4,5</sup>. Activated JAKs add a phosphate molecule to cell-surface receptors, which creates a binding site for STAT proteins<sup>4,5</sup>



**3** STAT proteins become activated by JAKs through the addition of another phosphate molecule<sup>4,5</sup>



**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<sup>4,5</sup>

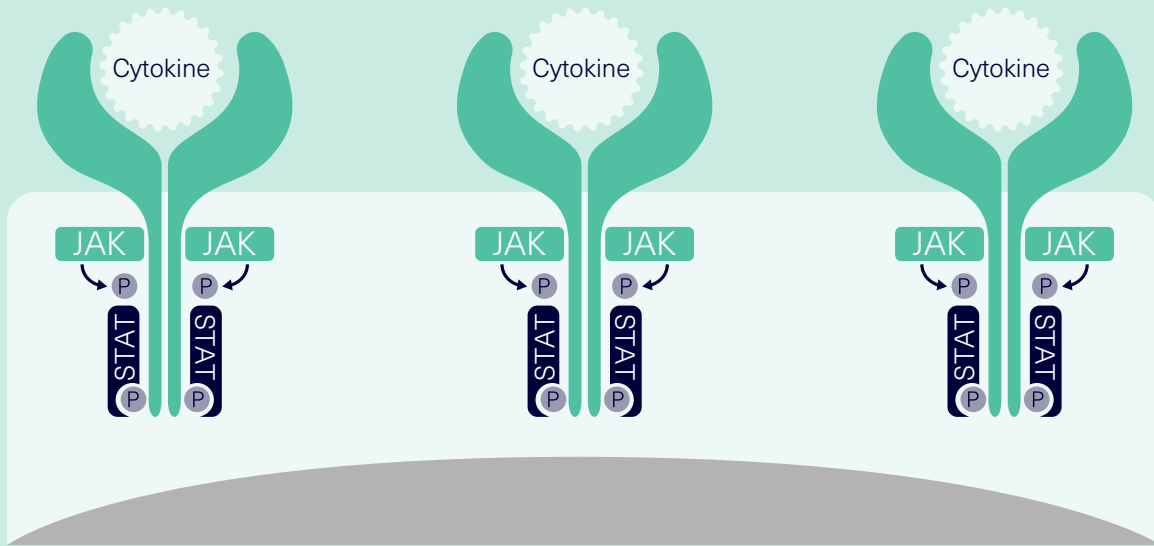


# An Altered JAK-STAT Pathway

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

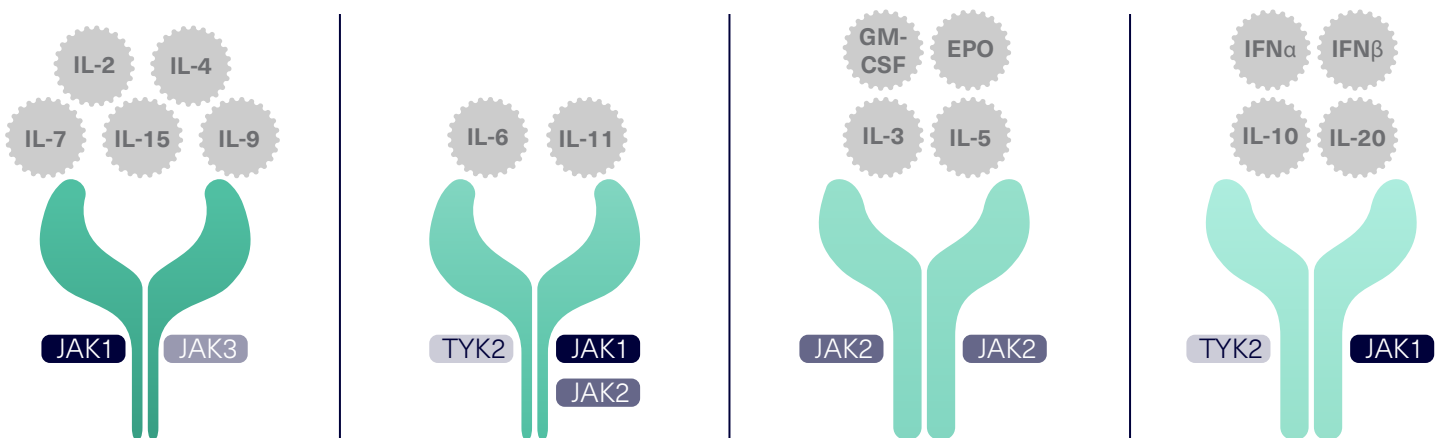
Overexpression of pro-inflammatory cytokines that activate JAK enzymes can lead to increased activation of the JAK-STAT pathway<sup>2,5</sup>

This increase in pro-inflammatory signaling disrupts the balance required for normal immune responses, resulting in the immune system attacking and damaging healthy tissue<sup>2,5</sup>



## 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.<sup>3</sup> 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 $\alpha$ / $\beta$ )<sup>3</sup>



\*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)].

**Selectively inhibiting certain JAKs may help control the overactivation of inflammatory signaling that is observed in certain immune-mediated diseases<sup>3</sup>**

1. ADA M Medical Encyclopedic. Immune Systems and Disorders. Available at: <https://medlineplus.gov/immunesystemanddisorders.html>. Accessed August 16, 2019. 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.