Exploring the JAK-STAT Pathway

JAK-STAT: What's That?

JAK-STAT signaling begins with cytokines binding to cell-surface receptors. STAT proteins become activated by JAKs through the addition of another phosphate molecule. 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.

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.
- **JAK enzymes**: Four types including JAK1, JAK2, JAK3, TYK2.
- **STAT proteins**: Seven types including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6.

Steps of JAK-STAT Signaling

1. JAK-STAT signaling begins with cytokines binding to cell-surface receptors.
2. After cytokine binding, specific JAK enzymes dimerize and become activated by binding ATP. Activated JAKs add a phosphate molecule to cell-surface receptors, which creates a binding site for STAT proteins.
3. STAT proteins become activated by JAKs through the addition of another phosphate molecule.
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.
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 pathway²,⁵.

This increase in pro-inflammatory signaling disrupts the balance required for normal immune responses, resulting in the immune system attacking and damaging healthy tissue²,⁵.

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 (IFNα/β).³

*Representation of common cytokine and receptor parings 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.³