The JAK/STAT Pathway: Fact Sheet

The JAK/STAT pathway plays a key role in blood cell production and immune and inflammatory responses in the body. Defects or overactivity in this pathway are thought to underlie various disease states, including myeloproliferative neoplasms (MPN), a group of diseases in which specific types of blood cells are overproduced and their functioning is disrupted. The JAK/STAT pathway may also be involved in the pathogenesis of conditions such as other types of cancers, rheumatologic and autoimmune disorders, and transplant rejections.[1]

Discovery and Roman Mythology
JAK proteins are members of the large family of enzymes called tyrosine kinases, which generally function as "on-off" switches for other proteins by attaching a phosphate molecule to them. The first gene for a JAK protein was cloned and sequenced in 1990.[2]

Scientists recognized JAK proteins as unique because they not only had an active tyrosine kinase site, but also a second "kinase-like" or "pseudokinase" site that helped control the first site. Because the two sites were joined together, researchers named the protein "Janus kinase", after the two-faced god Janus from Roman mythology. A number of members of the JAK family have been identified (e.g., JAK1, JAK2 and JAK3).[2]

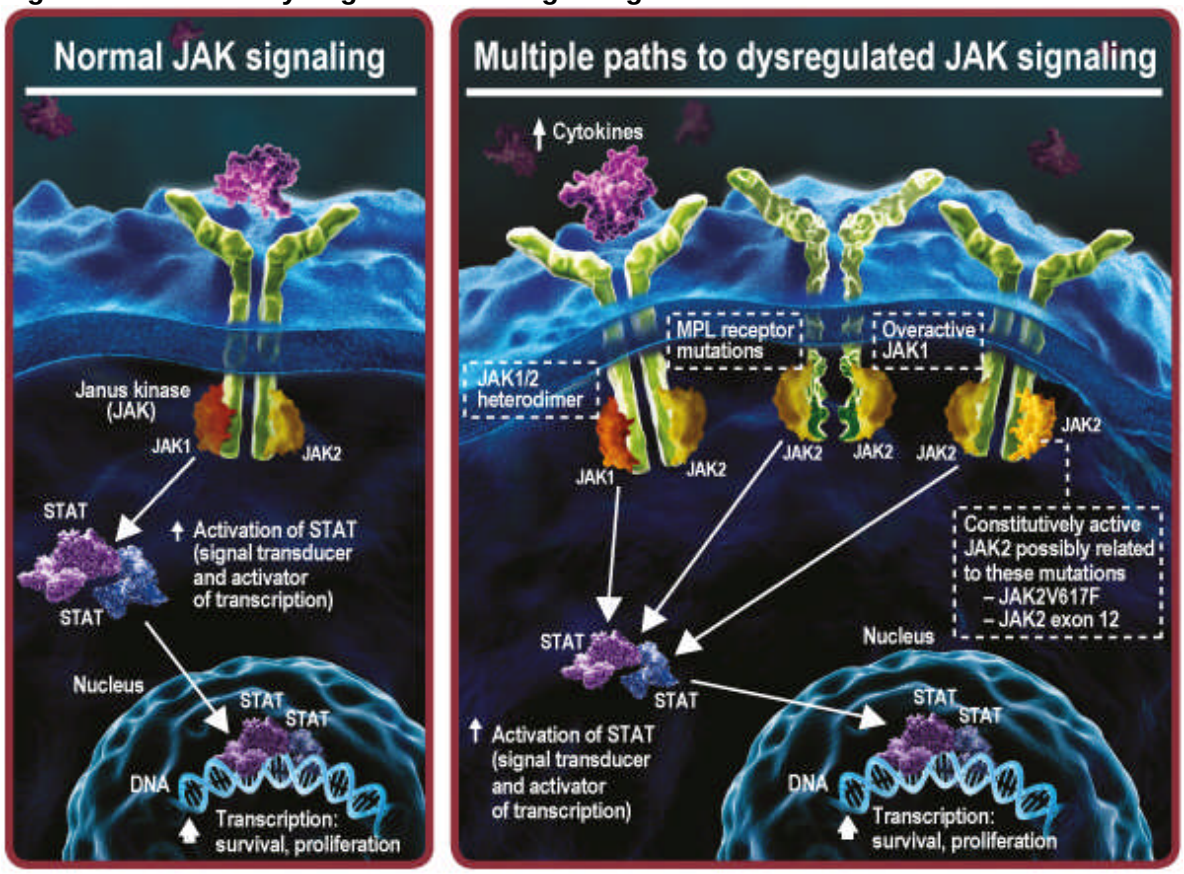
How the Pathway Works
The JAK/STAT pathway transmits signals from blood cell growth factors, cytokines (e.g., interleukin and interferon) or hormones outside a bone marrow stem cell to its nucleus. Under normal conditions, this ensures proper blood cell development and function, as well as balanced inflammatory responses.[3]

JAK/STAT proteins are key players in many important biological processes, including the regulation of immune function and the formation and development of blood cells.[3,4] Generally, blood cell growth factors work through JAK2, and pro-inflammatory cytokines work though JAK1 or JAK1 in combination with JAK2.[5]

JAK signaling involves the following sequence (see Figure):[2]

- A cytokine or blood cell growth factor binds to a receptor on the outside of a bone marrow stem cell.
- The two "legs" of the receptor close and activate the JAK protein inside the cell.
- The JAK protein adds phosphate groups to the receptor legs inside the cell, creating docking sites for STAT proteins.
- Once STAT proteins dock with the receptor, JAK activates the STAT proteins by adding phosphate groups to them.
- The activated STAT proteins go into the nucleus where they activate a gene that promotes blood cell production or inflammatory responses, depending on the specific JAK/STAT proteins involved.

Figure: Normal vs. Dysregulated JAK Signaling



Pathway Disruptions

Normally, the JAK/STAT pathway is tightly controlled to ensure normal blood cell production and function, but disruptions in the pathway can cause disease states. For example, in many patients with the myelofibrosis, a type of MPN, the JAK pathway is overactive as a result of mutation(s) affecting JAK or other proteins in the signaling chain.[6] Since overactive JAK signaling can affect both JAK1 and JAK2, it is associated with both inflammation and overproduction of blood cells, respectively.

While specific mutations in the JAK pathway have been established in relation to MPNs, it is believed the JAK pathway is overactive in all MPNs – which includes myelofibrosis, polycythemia vera, and essential thrombocythemia – regardless of whether a mutation has been identified.[5] Indeed, there is a strong association between abnormal cell signaling in the JAK pathway and the development of MPNs.[7]

Ongoing, Promising Research

Given the important role of the JAK/STAT pathway in blood cell production and immune and inflammatory processes, scientists are actively researching the potential of JAK inhibitors in treating MPNs, other types of cancers, rheumatologic and other autoimmune disorders, and transplant rejections.[1]

References

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