JAKs

Key References

Agaisse, H. and Perrimon, N., The roles of JAK/STAT signaling in *Drosophila* immune responses., *Immunol. Rev.*, **198**, 72-82 (2004).

Aringer, M., et al., Janus kinases and their role in growth and disease., *Life Sci.*, **64**, 2173-2186 (1999).

Ihle, J.N., Cytokine receptor signaling., *Nature*, **377**, 591-594 (1995).

Ihle, J.N. and Kerr, I.M., Jaks and Stats in signaling by the cytokine receptor superfamily., *Trends Genet.*, **11**, 69-74 (1995).

Imada, K. and Lenoard, W.J., The Jak-STAT pathway., *Mol. Immunol.*, **37**, 1-11 (2000).

Lacronique, V. and Boureux, A., et al., A TEL-JAK2 fusion protein with constitutive kinase activity in human leukemia., *Science*, **278**, 1309-1312 (1997).

Leonard, W.J. and O'Shea, J.J., Jaks and STATs: biological implications., *Annul. Rev. Immunol.*, **16**, 293-322 (1998).

Luo, C. and Laaja, P., Inhibitors of JAKs/STATs and the kinases: a possible new cluster of drugs., *Drug Discov. Today*, **9**, 268-275 (2004).

O'Shea, J.J., et al., Cytokine signaling in 2002: new surprises in the Jak/Stat pathway., *Cell*, **109**, S121-131 (2002).

Seidel, H.M., et al., Pharmaceutical intervention in the JAK/STAT signaling pathway., *Oncogene*, **19**, 2645-2656 (2000).

Shuai, K. and Liu, B., Regulation of JAK-STAT signaling in the immune system., *Nat. Rev. Immunol.*, **3**, 900-911 (2003).

Zhou, Y-J., et al., Unexpected effects of FERM domain mutations on catalytic activity of Jak3: structural implication for janus kinases., *Mol. Cell.*, **8**, 959-969 (2001).

Overview

The Janus kinases were initially identified as a novel subfamily of 120-140 kDa cytoplasmic tyrosine kinases that uniquely contained two, tandem domains with homology to tyrosine kinase catalytic domains. Initial insights into their roles in signal transduction came from genetic studies of interferon signaling and subsequently in biochemical studies of erythropoietin and growth hormone signaling. The most carboxyl-domain (JAK homology domain 1, JH1) has tyrosine kinase catalytic activity while the amino-terminal domain does not and is referred to as the pseudokinase domain (JH2). The amino-terminal half of the proteins contains the JH7-JH3 domains that are involved in receptor association, including a region (JH7-JH5) that contains a region with homology to a 300 amino acid protein-protein interaction domain referred to as the FERM domain (band four-point-one, ezrin, radixin, moesin domain).

The JAK family of kinases consists of four family members (JAK1, JAK2, JAK3, Tyk2) that each play unique roles in signal transduction. The major physiological roles of the JAKs are to initiate signal transduction through virtually all of the receptors of the cytokine receptor superfamily. The physiological roles of the JAKs have been most clearly illustrated through the derivation of mutant strains of mice lacking them. In particular, a deficiency of JAK2 causes loss of function of a variety of cytokine receptors including erythropoietin, thrombopoietin, growth hormone and prolactin, among a large number. Deficiency of JAK1 results in loss of function of most of the cytokine receptors that utilize receptors of the IL-6 cytokine receptor subfamily. Loss of Tyk2 results in some loss of interferon α/β signaling and a more profound loss of IL-12 signaling. As noted below a deficiency of JAK3 affects the IL-2 subfamily of cytokine receptors.

The JAKs physically interact through their FERM domains with the cytoplasmic, membrane proximal regions of the receptors through a loosely conserved region referred to as the Box 1/Box 2 region. The specificity of these interactions is largely responsible for the specificity of physiological functions of the JAKs. For example, JAK3 is only known to associate with the common γ chain of the IL-2 receptor complex and consequently mutations/deletions of the JAK3 specifically eliminate signaling through the IL-2 subfamily of cytokine receptors that utilize this receptor chain. In general single chain receptors require JAK2 or JAK1 for function while multi-chain receptors often require more than one JAK. For example, both JAK1 and JAK2 are required for interferon γ signal transduction while both JAK1 and JAK3 are required for the IL-2 receptor subfamily. The basis for the dependency on two JAKs in some receptor systems has not been established in biochemical detail. Receptor engagement results in changes in states of aggregation of the receptors, or conformation of their cytoplasmic domains, resulting in the trans-tyrosine phosphorylation of a regulatory site in the activation loop of the kinase domain causing mutual activation. Upon activation, the JAK kinases phosphorylate multiple sites on the kinase itself, on the receptor chains and substrates that are recruited to the receptor complex.

One of the common substrates of the JAK kinases in cytokine signaling are members of the signal transducers and activators of transcription (Stats) although a wide variety of signal transducing proteins have been shown to be phosphorylated by the JAKs in cytokine signaling. In humans, mutations of JAK3 are associated with genetically acquired severe combined immunodeficiency. Because of its importance in signaling by receptors controlling lymphoid cells, considerable interest has existed in defining specific inhibitors as immunoregulatory compounds. The activation of JAKs is frequently implicated in oncogenic transformation and human chromosomal translocations resulting in the activation of JAK2 have been identified. Although JAK activation has been reported in non-cytokine receptor superfamily receptor systems including both receptor tyrosine kinase and G protein-coupled receptor systems, the physiological relevance of this activation has not been definitively established through the use of the mutant strains of mice lacking JAKs.

JAKs

Family Members	JAK1	JAK2	JAK3	TYK2
Other Names	Janus kinase 1	Janus kinase 2	Janus kinase 3	Tyrosine kinase 2
Molecular Weight/ Structural Data	132 kDa, 1142 aa	131 kDa, 1132 aa	125 kDa, 1124 aa	134 kDa, 1182 aa
Isoforms	Not known	Not known	JAK3M, JAK3B, JAK3S	Not known
Species	Vertebrate, mammalian, rat, mouse metazoa, plants, fungi, *Drosophila*	Vertebrate, mammalian, rat, mouse metazoa, plants, fungi, *Drosophila*	Vertebrate, mammalian, rat, mouse metazoa, plants, fungi, *Drosophila*	Human, mouse
Domain Organization	7 JH homology domains, JH1 kinase domain, JH2 pseudokinase domain	7 JH homology domains, JH1 kinase domain, JH2 pseudokinase domain	7 JH homology domains, JH1 kinase domain, JH2 pseudokinase domain	7 JH homology domains, JH1 kinase domain, JH2 pseudokinase domain
Phosphorylation Sites	Tyr^{1022}, Tyr^{1023}, Tyr^{1033}	Tyr^{1007}, Tyr^{1008}	Tyr^{1033}, Tyr^{980}, Tyr^{981}	Tyr^{1054}, Tyr^{1055}
Tissue Distribution	Ubiquitous	Ubiquitous	Hematopoietic	Ubiquitous
Subcellular Localization	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm, nucleus
Binding Partners/ Associated Proteins	Cytokine receptors, growth factor receptors	Cytokine receptors, growth factor receptors	Common γ chain	Cytokine receptors, growth factor receptors
Upstream Activators	IFNα, **(I4401)**, IFNγ **(I1520)**, IL-2 **(I2644, I7908** (h)**)** IL-4 **(I4269** (h)**)**, IL-9 **(I3394** (h)**)** IL-13 **(I1771** (h)**)**, IL-15 **(I8648)**, IL-3 **(I1646, I7389** (h)**)**, IL-6 **(I1395)**, OSM **(O9635)** IL-11 **(I2406)**, CT-1, CNTF **(C3710)**, LIF **(L5283)**, OSM **(O9635)**, prolactin **(L7009)**	IFNγ **(I1520)**, EPO **(E5627)**, IL-3 **(I1646, I7389** (h)**)**, IL-5 **(I5273)**, GM-CSF **(G5035)**, IL-6 **(I1395)**, IL-11 **(I2406)**, CT-1, CNTF **(C3710)**,	IL-2 **(I2644, I7908** (h)**)**, IL-4 **(I4269** (h)**)**, IL-7 **(I5896** (h)**)**, IL-9 **(I3394** (h)**)**, IL-15 **(I8648)**	IFNα **(I4401)**, IL-12 **(I2276)**, IL-13 **(I1771** (h)**)**, IL-6 **(I1395)**, IL-11 **(I2406)**, OSM **(O9635)**, CNTF **(C3710)**, LIF **(L5283)**, CT-1
Downstream Activation	STATs/multiple pathways	STATs/multiple pathways	STATs/multiple pathways	STATs/multiple pathways
Activators	Not known	Not known	Not known	Not known
Inhibitors	Not known	AG490 **(T3434)**	CP-690550 JANEX-1 **(W0513)** PNU15680	Not known
Selective Activators	Not known	Not known	Not known	Not known
Physiological Functions	Involved in interferon α/β/γ signaling pathway	Signal transduction by multiple cytokines	Signal transduction by IL-2 family cytokines	Involved in initiation of type I IFN signaling
Disease Relevance	Tumorigenesis, leukemias, myocardial ischemia	Diseases of abnormal erythro-poiesis, myeloproliferative disorders immunosuppressive diseases	Severe combined immunodeficiency, lympho-proliferative disorders	Immune diseases

Footnotes