Targeting the JAK/STAT Pathway

Technical Bulletin

JAK-STAT Signaling - *Key Roles in Hematological Cancers*

Source: Allan Mah, PhD. Product Manager - SignalChem

Hematopoiesis is the process of blood cell proliferation and differentiation from hematopoietic stem cells (HSCs). The stem cell population is renewed via self-replication and they differentiate into to daughter myeloid and lymphoid cell lines. Myeloid progenitors give rise to erythrocytes, and cells that are involved in both innate and adaptive immunity. These cells include: monocytes, macrophages, neutrophils, basophils, eosinophils, megakaryocytes/platelets and dendritic cells. The lymphoid cell line gives rise T-cells, B-cells and NK-cells; all critical components of adaptive immunity in mammals.

The decision of HSCs to enter quiescence, renew, differentiate, mature, undergo apoptosis or proliferate is largely under the control extrinsic signaling cues, which often take the form of growth factors and cytokines. Under normal conditions, white blood cell proliferation is essential for immunological responses. However, dysregulation of this process leads to hematological cancers such as leukemia, lymphoma. Lymphoma arises from lymphoid tissue and the disease is divided into two main categories: Hodgkin's disease and non-Hodgkin's lymphoma. Leukemia is characterized by excess proliferation of blood cells of either Lymphoblastic or Myeloid cells. Myeloma occurs when plasma cells undergo uncontrolled divisions within the bone marrow.

The Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway is essential for coordinating the mechanisms underlying, hematopoiesis and other processes such as adipogenesis and immunity. The JAK/STAT pathway is the main signaling mechanism for cytokines: When cytokines bind to membrane-bound receptors, JAK proteins activate themselves and their receptors through phosphorylation, which in turn then recruits STAT transcription factors. Once activated, the STAT transcription factors dimerize and translocate to the nucleus where they activate and repress target gene expression. STAT transcription factors control a wide range of physiological processes though different homo- and hetero-dimer pairings (1). Dysregulation of any component within the carefully coordinated JAK/STAT pathway can lead to hematopoietic cancers (2).

Mutations that constitutively activate the JAK/STAT pathway are common in hematological cancers (3,4): TEL-JAK2 results from the fusion of the dimerization domain of TEL with the catalytic domain of JAK2. Induced dimerization causes the fusion protein to auto-activate. A single amino acid change in the JAK2 (V617F) protein creates a defective inhibitory domain within the protein. This mutation is frequently observed in BCR-ABL1-negative myeloproliferative neoplasms (MPNs). Therefore, the JAK2 (V617F) is emerging as an important target for the drug development (5).

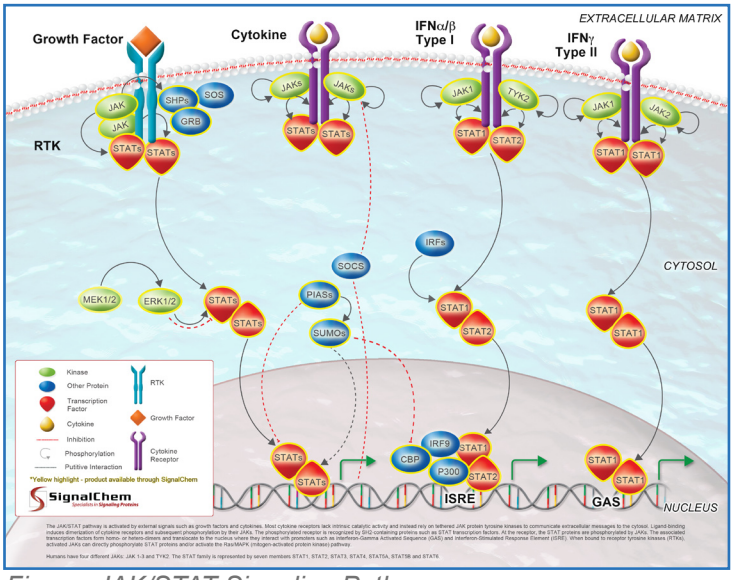


Figure: JAK/STAT Signaling Pathway

SignalChem manufactures Active Kinases for all four JAK kinases along with Recombinant Proteins for all seven STAT transcription factors. In addition, other Inhibitory Compounds, siRNAs, Antibodies, Cytokines, Growth Factors, Active Enzymes and Recombinant Proteins are available to facilitate comprehensive studies and drug-development efforts that target the JAK/STAT pathway.

References:

1. Delgoffe GM and Vignali DA., STAT heterodimers in immunity: A mixed message or a unique signal? JAKSTAT. 2013 Jan 1;2(1):e23060. doi: 10.4161/jkst.23060.

2. Ferrajoli A et al., The JAK-STAT pathway: a therapeutic target in hematological malignancies. Curr Cancer Drug Targets. 2006 Dec;6(8):671-9.

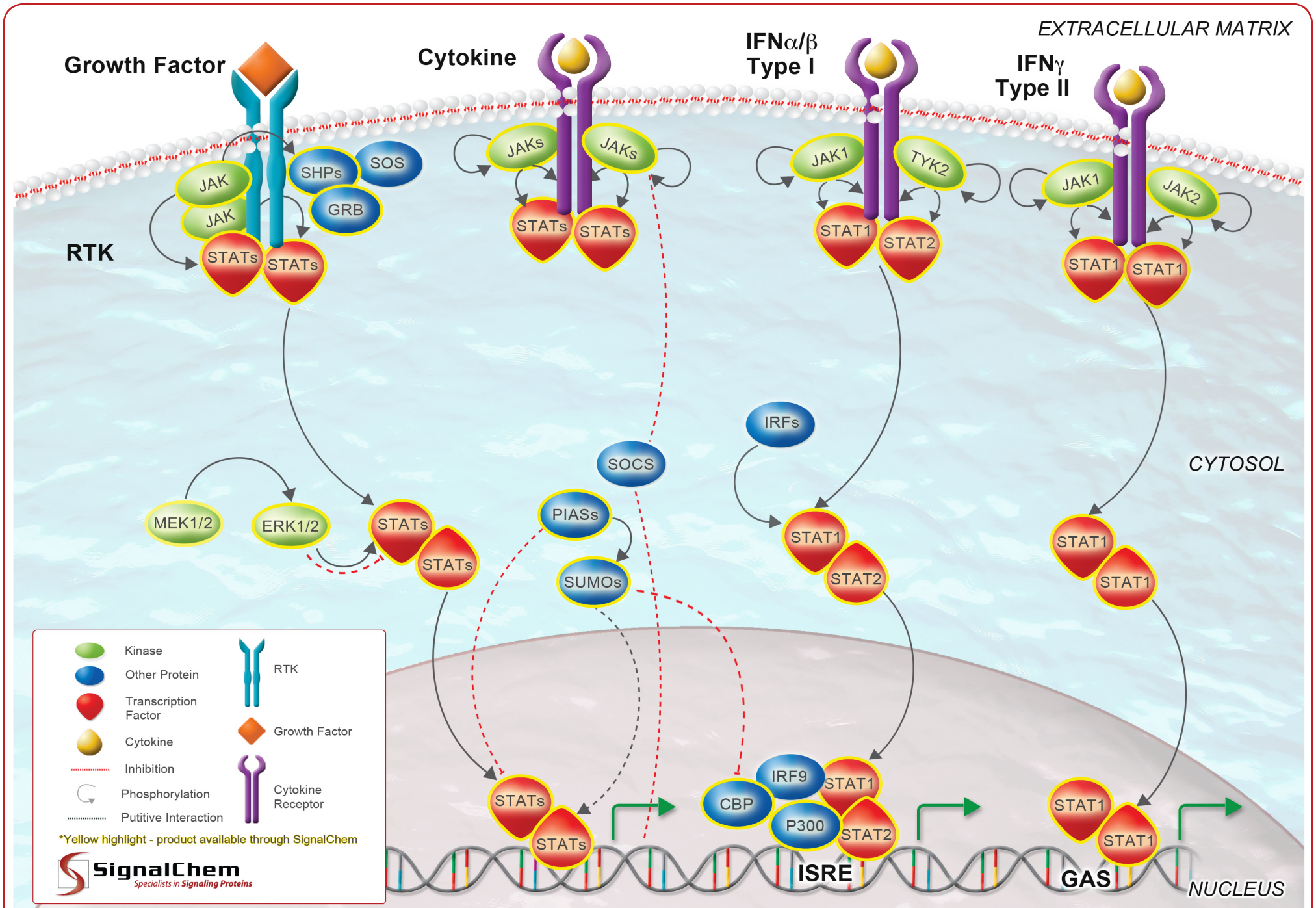
3. Toms AV et al., Structure of a pseudokinase-domain switch that controls oncogenic activation of Jak kinases. Nat Struct Mol Biol. 2013 Oct;20(10):1221-3. doi: 10.1038/nsmb.2673.

4. Pasquier et al., Myeloproliferative Neoplasms: JAK2 Signaling Pathway as a Central Target for Therapy. Clin Lymphoma Myeloma Leuk. 2014 Sep;14S:S23-S35. doi: 10.1016/j.clml.2014.06.014.

5. Pardanani A et al., JAK inhibitor therapy for myelofibrosis: critical assessment of value and limitations. Leukemia (2011) 25, 218–225; doi:10.1038/leu.2010.269

SignalChem
Specialists in Signaling Proteins

www.signalchem.com
Tel: 1.866.954.6273
info@signalchem.com



The JAK/STAT pathway is activated by external signals such as growth factors and cytokines. Most cytokine receptors lack intrinsic catalytic activity and instead rely on tethered JAK protein tyrosine kinases to communicate extracellular messages to the cytosol. Ligand-binding induces dimerization of cytokine receptors and subsequent phosphorylation by their JAKs. The phosphorylated receptor is recognized by SH2-containing proteins such as STAT transcription factors. At the receptor, the STAT proteins are phosphorylated by JAKs. The associated transcription factors form homo- or hetero-dimers and translocate to the nucleus where they interact with promoters such as interferon-Gamma Activated Sequence (GAS) and Interferon-Stimulated Response Element (ISRE). When bound to receptor tyrosine kinases (RTKs), activated JAKs can directly phosphorylate STAT proteins and/or activate the Ras/MAPK (mitogen-activated protein kinase) pathway.

Humans have four different JAKs: JAK 1-3 and TYK2. The STAT family is represented by seven members STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6.