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SMARTImmunology

The Immunology Newsletter from SMARTANALYST

JAK-STAT Pathway - Role in Immunology

The Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway is a signaling pathway employed by over 50 cytokines, interferons, growth factors, and related molecules to control gene expression. It serves as a fundamental paradigm for how cells sense environmental signals and interpret these signals to stimulate cell proliferation, differentiation, activation/inhibition and survival/apoptosis. These cellular events are critical to hematopoiesis, immune development, mammary gland development and lactation, adipogenesis, sexually dimorphic growth and other processes.

JAK-STAT signaling involves sequential receptor recruitment and activation of members of the JAKs and the STATs to control transcription of target genes via specific response elements. Several cytokines use JAK-STAT signaling direct transcription through specific but not necessarily unique combinations of JAKs and STATs. Although specific STATs appear to be dedicated to specific subsets of cytokine signaling, the same STAT or combination of STATs can be activated in different cytokine systems to give completely different biological effects.

The JAK-STAT signaling pathway consists of:

- 4 Janus kinases (JAK1, JAK2, JAK3 and Tyk2)
- 7 Signal transducer and activator of transcription (STAT)
- 3 Protein tyrosine phosphatase (SHPs)
- 4 Protein inhibitors of activated STATs (PIAS)
- 8 Suppressors of cytokine signaling (SOCS)

JAK-STAT pathway activation

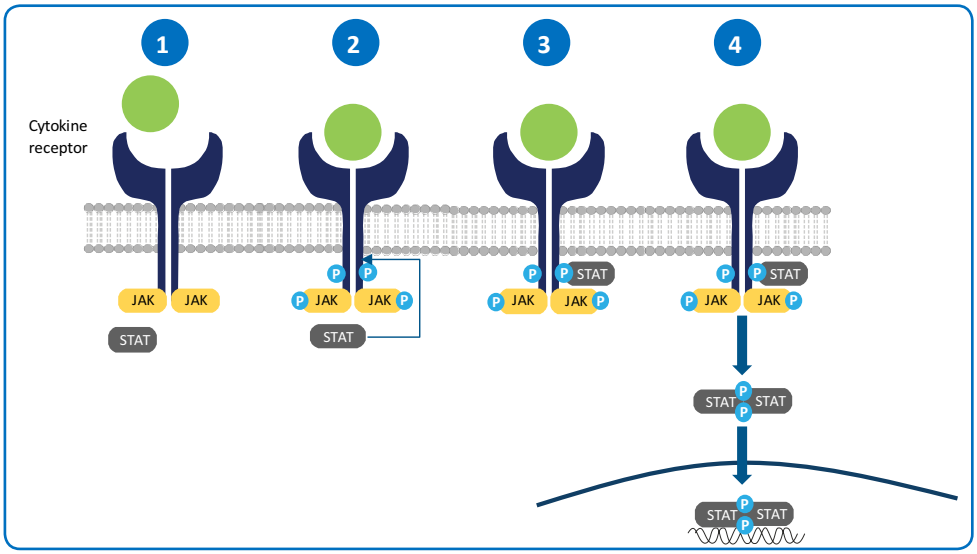

Figure 1: (1) When a cytokine engages its receptor, JAKs become activated and phosphorylate each other, as well as the intracellular tail of their receptors. (2) This creates a docking site for STATs, which are now able to bind to the cytoplasmic domain of the receptor. (3) The STATs, in turn, are phosphorylated and activated, which allows them to dimerize. (4) The STAT-STAT dimer translocates to the nucleus, where it can directly bind DNA and regulate gene expression

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JAK-STAT pathway – Key activators, effectors and regulators

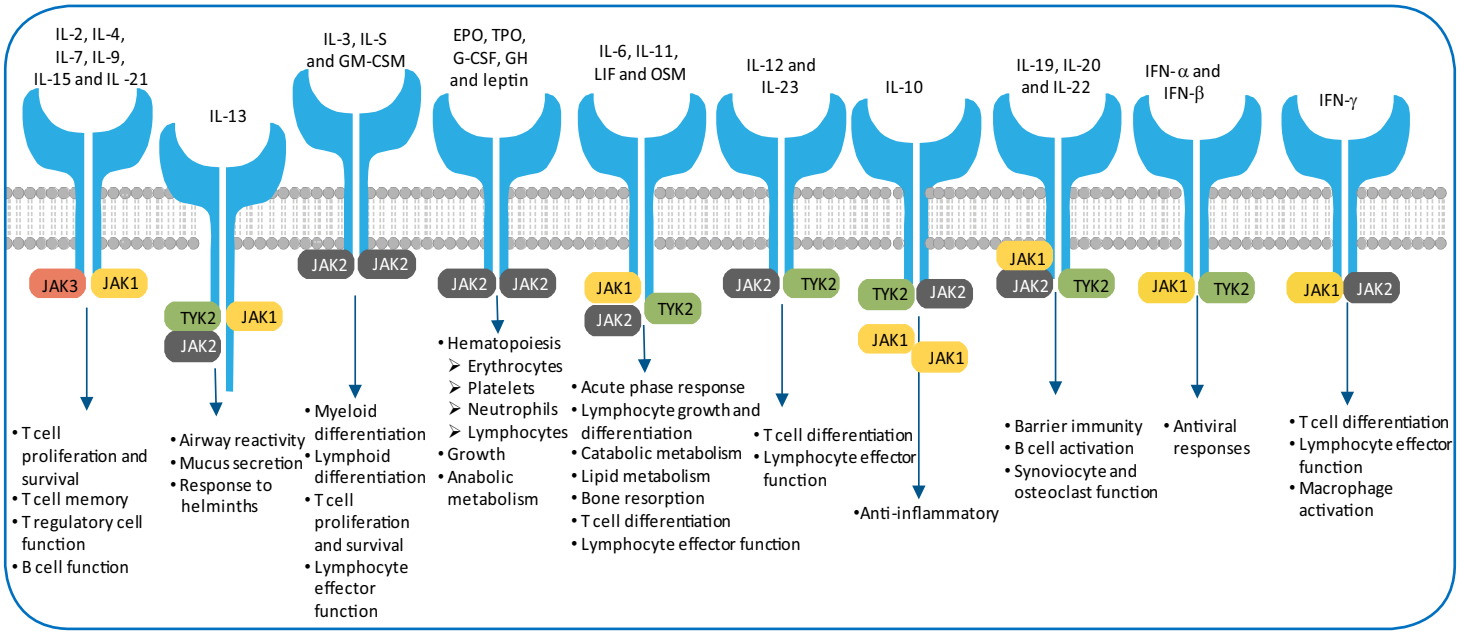
Activators	Effectors	Regulators
Cytokines hormones growth factors interferons (IFNs)	**STAMs (Signal-transducing adapter molecules)** *- facilitate the transcriptional activation of specific target genes, including MYC*	**SOCS (Suppressors of cytokine signaling)** *- complete a simple negative feedback loop in the JAK-STAT pathway*
	STATIP (STAT-interacting protein) - *can associate with both JAKs and unphosphorylated STATs, perhaps serving as a scaffold to facilitate the phosphorylation of STATs by JAKs*	**PTPs (Protein tyrosine phosphatases) -** *reverse the activity of the JAKs; SHP-1 can bind to either phosphorylated JAKs or phosphorylated receptors to facilitate dephosphorylation of these activated signaling molecules*
	SH2B/Lnk/APS family - *SH2-Bb facilitates JAK-STAT signaling while the APS associated with JAKs inhibits it*	**PIAS (Protein inhibitors of activated stats) -** *bind to activated STAT dimers and prevent them from binding DNA*

The functions of activated STATs can be altered through association with transcription factors {c-Jun, Interferon Regulatory Factor-9 (IRF9), c-Fos, Nuclear Factor-KappaB (NF-KB), SMAD (Sma and Mad [mothers against decapentaplegic] Related Protein Transcription Factor SP1 (SP1))} and cofactors {p300, CREB-binding protein (CBP), Breast Cancer-1 gene (BRCA1), and Minichromosome Maintenance-5 (MCM-5)} that are regulated by other signaling pathways.

JAK-STAT pathway – Role in immune system regulation and association with disorders

The JAK-STAT pathway plays a critical role in initiation and regulation of innate immune responses and adaptive immunity from resisting infection to maintaining immune tolerance, enforcing barrier functions, and guarding against cancer. Disturbance of the JAK-STAT pathway often leads to immunological and hematopoietic diseases as well as various cancers. Mutations that reduce JAK-STAT pathway activity generally lead to a compromised immune system and conversely, mutations that activate or fail to regulate JAK signaling properly contribute to proliferative disorders and malignancies.

Role of JAK-STAT pathway in immune system regulation

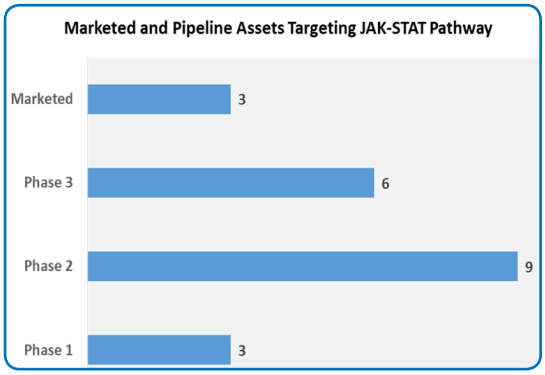


Mutations and polymorphisms in *JAK* and *STAT* genes have been linked with several human diseases and the variety of pathology caused by these mutations dramatically illustrates the criticality of JAK-STAT signaling both for normal and aberrant immune responses. JAK-dependent cytokines are major contributors to immunopathology. For instance, IL-6 is a prototypic pro-inflammatory cytokine commonly overexpressed in many autoimmune and inflammatory diseases. Similarly, overexpression of IL-4, IL-5 and IL-13 is seen in allergic disease. Other JAK-dependent cytokines contributing to inflammatory diseases include IFNs, IL-15, IL-21, granulocyte-CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF).

JAK-STAT pathway modulation – Targets and assets

The development of agents targeting cytokines or their receptors (e.g. anti-TNFs, IL-6 inhibitors), represents a landmark advancement in the treatment of autoimmune and inflammatory diseases. Despite the therapeutic success of these drugs, it has become evident that targeting a single cytokine is not efficacious for all patients with an immunologic disease.

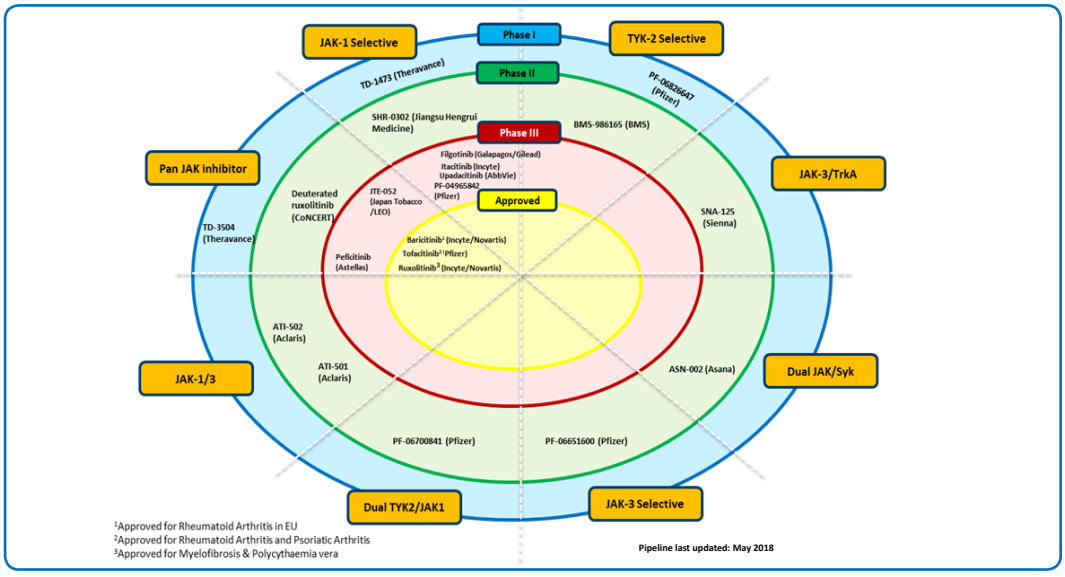
If targeting specific cytokines outside the cell is insufficient to reliably achieve complete remission, an obvious alternative strategy is to target the action of different cytokines inside the cell. Understanding the intracellular pathways downstream of cytokine receptors has led to the inhibition of intracellular enzymes (e.g. JAK family of enzymes) such as receptor-associated kinases representing a novel way to simultaneously inhibit multiple cytokines.



Building on the clinical success of first-generation jakinibs, second-generation compounds that claim to be more selective, are currently undergoing development. Moreover, novel mechanisms of achieving high selectivity are emerging. All current jakinibs act on JAKs through noncovalent interactions with the kinase domain, which is relatively conserved between isoforms, but several novel compounds have been reported to bind covalently to nonconserved amino acid residues. This leads to irreversible inhibition and reportedly high selectivity across the kinome.

Small-molecule inhibitors of JAKs (jakinibs) have emerged as options for the treatment of inflammation driven pathologies such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.

Marketed and pipeline JAK-STAT inhibitors



JAK-STAT pathway modulation – Safety considerations

The safety profile of JAK inhibitors is largely similar to that of biologic agents, including risk of infection and malignancy. However, specific differences exist with regard to cellular changes and risk of certain types of infections, notably viral diseases such as herpes zoster.

There is an overlap in the safety profile between jakinibs despite differences in selectivity. Jakinibs are associated with neutropenia, anemia and thrombocytopenia, and increase in lipid, liver transaminase and serum creatinine levels. However, it was observed during

the development program of tofacitinib and baricitinib, that only a small percentage of patients developed serious adverse events attributable to changes in laboratory parameters. A few differences have been observed among Jakinibs in terms of laboratory changes – there is an increase in platelet and lymphocyte counts with baricitinib, while tofacitinib is associated with decreased platelet and lymphocyte counts. However, the available data is not conclusive enough to attribute these changes to JAK selectivity.

There have been recent concerns about potential thromboembolic risks with jakinibs. An FDA advisory committee recommended against the approval of the higher dose of baricitinib (4 mg/day) due to higher risk of thromboembolic events. A recent systematic review of the FDA's Adverse Event Reporting System (FAERS) found elevated reporting for both tofacitinib and ruxolitinib for thromboembolic adverse events, suggesting the possibility of a class-wide issue with JAK inhibitors.

JAK-STAT pathway modulation – Future directions

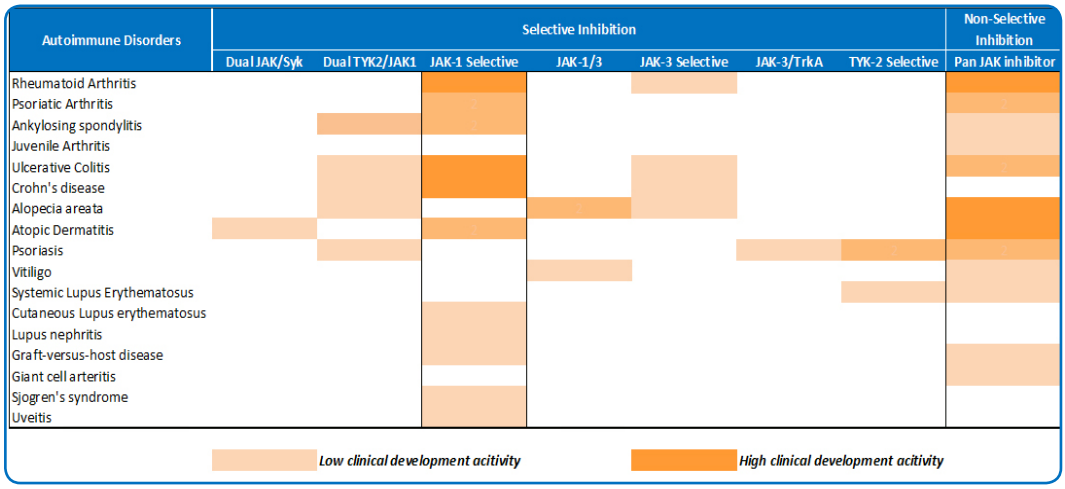
Several jakinibs are currently in clinical development for a spectrum of autoimmune disorders – autoimmune joint diseases, inflammatory bowel disorders (IBDs), autoimmune dermatological diseases and multisystem diseases such as lupus. Jakinibs are in the most advanced phase of development in autoimmune joint diseases, with tofacitinib and baricitinib (in EU only) approved for RA. Tofacitinib is also approved for the management of moderately to severely active ulcerative colitis in the US.

Both selective and nonselective JAK inhibition strategies are under evaluation for autoimmune diseases. JAK-1 selective inhibition is the most common strategy under evaluation for multiple diseases including autoimmune joint diseases, IBD, lupus, atopic dermatitis, and GvHD.

Some patients with autoimmune diseases develop limited cutaneous, mucosal or ocular manifestations that can potentially be treated with a topical therapy. Topical formulations of ruxolitinib, tofacitinib (Aclaris), and delgocitinib are under investigation for various dermatological diseases such as psoriasis, atopic dermatitis, and alopecia areata.

Benefits, risks and optimal mechanisms to achieve in vivo selectivity remain elusive – clinical data for many selective jakinibs is still unavailable. Although current clinical data indicates that selective and non-selective jakinibs are equally effective for the treatment of rheumatoid arthritis, that may not be true for other autoimmune diseases. Based on current clinical data, it appears that JAK1-selective compounds may be more effective in Crohn's disease than was tofacitinib.

Selective/nonselective JAK inhibition strategies for key autoimmune diseases



Overall, JAK inhibitors represent an important addition to the therapeutic armamentarium for autoimmune diseases and are likely to partially fulfill the residual unmet need. However, some questions still remain unanswered. These include importance of specificity in inhibition, potential development of resistance to JAK inhibition, risk of thromboembolic events and relative risks and benefits in combination with cDMARDs or biologics.

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