

The JAK-STAT Pathway: Impact on Human Disease and Therapeutic Intervention*

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Abstract

The Janus kinase (JAK)–signal transducer of activators of transcription (STAT) pathway is now recognized as an evolutionarily conserved signaling pathway employed by diverse cytokines, interferons, growth factors, and related molecules. This pathway provides an elegant and remarkably straightforward mechanism whereby extracellular factors control gene expression. It thus serves as a fundamental paradigm for how cells sense environmental cues and interpret these signals to regulate cell growth and differentiation. Genetic mutations and polymorphisms are functionally relevant to a variety of human diseases, especially cancer and immune-related conditions. The clinical relevance of the pathway has been confirmed by the emergence of a new class of therapeutics that targets JAKs.

INTRODUCTION: A MOSTLY SIMPLE MEMBRANE-TO-NUCLEUS PATHWAY

Effective communication between cells is central to development, tissue and organism homeostasis, and host defense. Evolution has provided a number of elegant solutions to this problem, but among these the JAK-STAT pathway is one of the architecturally simplest paradigms, allowing direct communication from transmembrane receptors to the nucleus (**Figure 1**). Pioneering work on the control of gene expression by interferons led to the discovery of this pathway; however, it is now recognized that a wide variety of cytokines, colony-stimulating factors, and hormones employ this mode of signal transduction (**Table 1**).

Upon engagement by ligand, receptor-associated Janus kinases (JAKs) become activated and phosphorylate both each other and the intracellular tail of their receptors, thereby creating docking sites for latent, cytoplasmic transcription factors termed signal transducers and activators of transcription (STATs). JAK-mediated phosphorylation activates STATs, which in turn directly bind DNA and regulate gene expression (1, 2). There are four JAKs, named JAK1, JAK2, JAK3, and TYK2, which selectively bind different receptor chains (**Figure 2**). The selective usage of JAKs by different receptors explains their distinct *in vivo* roles (**Table 1**) and becomes particularly important with the generation of pharmacologic inhibitors when specific or relatively discrete functional outcomes are sought.

Seven mammalian STAT family members have been identified (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6). Different cytokines have the propensity to activate a

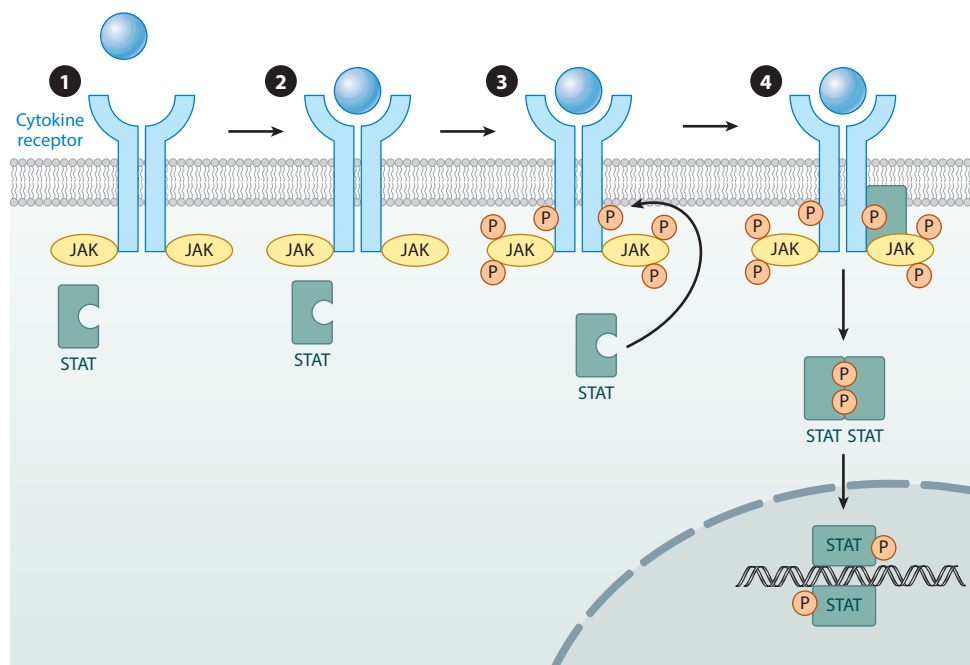


Figure 1

(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.

Table 1 JAKs and STATs with associated cytokines and phenotypes

JAK/STAT	Important for signaling by	Knockout mouse phenotype	Genetic links to human disease
JAK1	IFN α/β , IFN- γ , IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, IL-6 family cytokines, IL-10 family cytokines	Perinatally lethal	GOF somatic mutations cause ALL, AML, solid-organ malignancies
JAK2	IFN γ , IL-3, IL-5, GM-CSF, EPO, TPO, G-CSF, GH, leptin	Embryonically lethal due to absence of erythropoiesis	GOF mutations cause PV, PMF, ET, hypercoagulable state; somatic mutations associated with acute and chronic hematologic malignancies
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	Defective T and B cell maturation	LOF mutation causes severe combined immunodeficiency (SCID)
TYK2	IFN α/β , IL-12, IL-23	Reduced responses to type 1 interferon and IL-12, and defective Stat3 activation	LOF mutation causes primary immunodeficiency
STAT1	All interferons	Impaired responses to type 1 and 2 interferon	LOF mutations confer susceptibility to mycobacterial and viral infections; GOF mutations cause chronic mucocutaneous candidiasis
STAT2	Type I IFNs	Impaired response to type 1 interferon and susceptibility to viral infections	Deficiency causes increased susceptibility to viral mutations
STAT3	IL-6 and other gp130 cytokines	Embryonically lethal	LOF mutations cause AD-HIES; GOF somatic mutations strongly associated with LGL
STAT4	IL-12, IL-23, type 1 interferons	Mutations in mouse inhibit Th1 differentiation	Polymorphisms associated with RA, SLE
STAT5a/STAT5b	IL-2, EPO, TPO, GM-CSF, GH, IL-7	Defective hematopoiesis, other defects	Deficiency causes autoimmunity, bleeding diathesis, immunodeficiency, and dwarfism; somatic mutations associated with LGL
STAT6	IL-4, IL-13	Mutations in mouse inhibit T helper 2 differentiation	Polymorphisms associated with asthma, atopy, increased levels of IgE

Abbreviations: AD-HIES, autosomal dominant hyperimmunoglobulin E syndrome; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GOF, gain of function; ET, essential thrombocytosis; LGL, large granular lymphocytic leukemia; LOF, loss of function; PMF, primary myelofibrosis; PV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

particular STAT; however, interactive promiscuity between cytokines and any given STAT operates to varying degrees. The mechanisms by which STATs influence gene transcription have been elucidated using a combination of genetic approaches (e.g., use of knockout mice; see **Table 1**) and new technologies that allow genome-wide assessment of gene expression and transcription factor binding. It is now clear that STATs bind tens of thousands of sites in the genome and regulate transcription of thousands of protein-coding genes, along with microRNAs and long noncoding RNAs. STATs also have important impacts on chromatin structure and the distinctive enhancer landscapes of differentiating cells.

Although the aforementioned pathway is critical for the action of many cytokine and hormone receptors, it is important to recognize some inherent complexities. First, pathways other than STATs are activated by cytokines, and other (non-cytokine-mediated) pathways can influence the

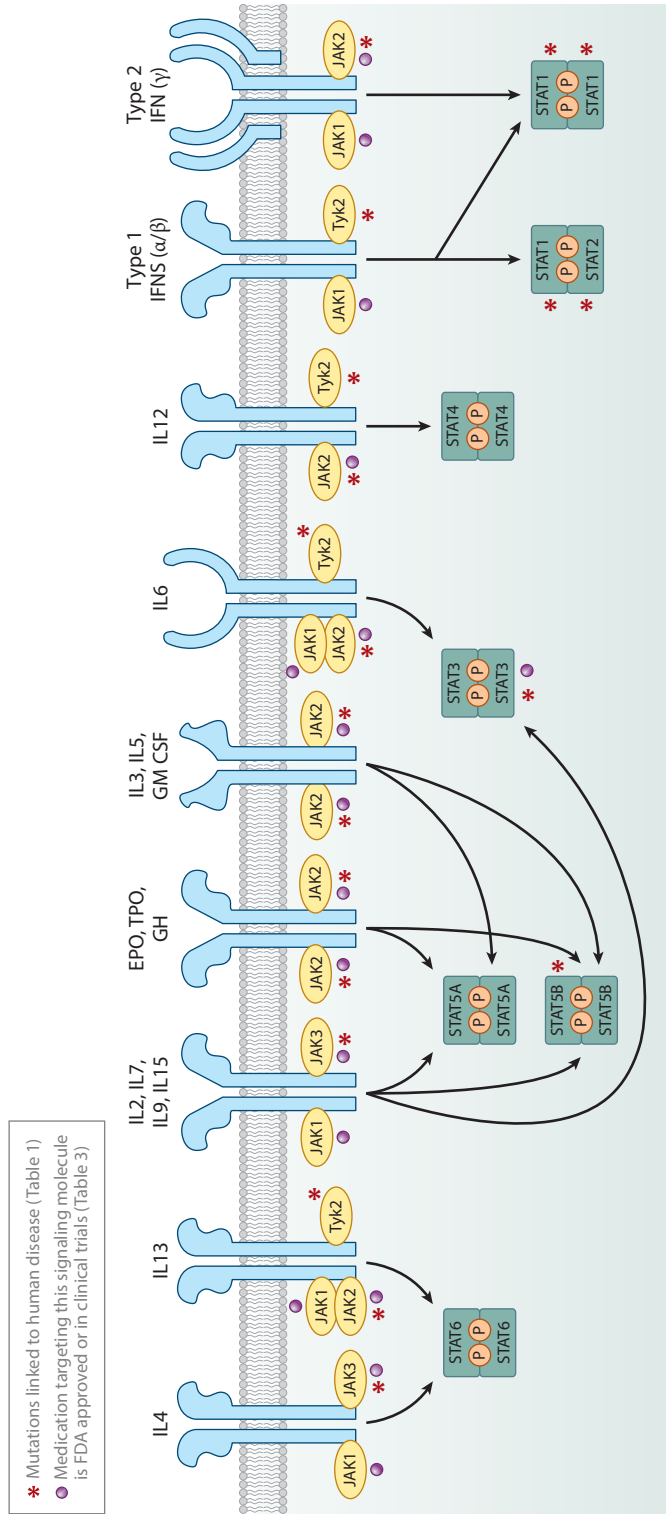


Figure 2

The four JAKs (JAK1, JAK2, JAK3, TYK2) are selectively bound to and therefore mediate signaling for various cytokine and hormone receptors. Different cytokines also have a propensity to activate certain STATs. Mutations in many of the genes encoding JAKs and STATs (indicated by an asterisk) have been linked to human disease. Details of the mutation and disease phenotype are in **Table 1**. A large number of medications targeting JAKs and, to a lesser degree, STATs (indicated by a •) are being developed and used to treat human disease. Details are in **Table 3**.

activation of STATs. Growth factors such as epidermal growth factor can induce STAT tyrosine phosphorylation, whereas other pathways induce STAT serine phosphorylation. Additionally, a number of functions have been ascribed to “unphosphorylated” STATs, and STATs have non-nuclear functions. STAT3 in particular localizes to mitochondria, where it is thought to promote oxidative phosphorylation and membrane permeability. Conversely, JAKs can also have actions in the nucleus independent of STATs, including phosphorylation of histone proteins. In summary, although a straightforward view of the JAK-STAT signaling pathway explains a great deal of cytokine biology, it is equally important to recognize the complexities.

GENETIC LINKS BETWEEN THE JAK-STAT PATHWAY AND HUMAN DISEASE

Several disorders of primary immunodeficiency, discussed individually below, have been linked to known mutations of JAKs and STATs.

Severe Combined Immunodeficiency

Perhaps the most dramatic evidence for the criticality of JAKs and STATs comes from patients with mutations in genes encoding these signaling molecules. Severe combined immunodeficiency (SCID) is a devastating primary immunodeficiency in which the combination of nonfunctional T cells and defective immunoglobulin production results in a syndrome of recurrent severe infection, diarrhea, atopic dermatitis, and failure to thrive. An important immunopathologic mystery was solved when mutations of a shared or common cytokine receptor subunit termed the common γ chain or γ_c were found to underlie X-linked SCID (1). In the absence of this receptor subunit, lymphocytes are unable to respond to IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 (**Figure 2**), severely impacting the development of T cells and NK cells and the function of B cells. Because JAK3 selectively associates with γ_c , mutations of *JAK3* have the same consequence.

In its classic presentation, the diagnosis of SCID is not difficult. However, not all cases are clinically obvious, and the ability to test for a specific genetic mutation can be useful in establishing a diagnosis. Moreover, identification of the disease-causing mutations has major therapeutic implications. SCID is considered a pediatric emergency, necessitating rapid hematopoietic stem cell transplantation (HSCT). However, if a compatible donor is not available, gene therapy might be a reasonable alternative. This approach was effective in addressing primary immune deficiency (2, 3), but clinical trials were complicated by leukemia due to insertional oncogenesis (3, 4). Nonetheless, newer technologies hold future promise for this approach.

Hyperimmunoglobulin E Syndrome

Hyperimmunoglobulin E syndrome (HIES, or Job's syndrome) is a multisystem disorder characterized by recurrent and severe cutaneous and sinopulmonary bacterial infections, chronic dermatitis, elevated serum immunoglobulin E (IgE), and connective tissue abnormalities. Underlying many cases of autosomal dominant HIES are dominant negative mutations of *STAT3* (5, 6). *STAT3* mediates signaling through at least six classes of receptors (7) (**Table 1**, **Figure 2**), explaining the range of immunologic and somatic abnormalities associated with this disorder. Many of the host defense deficits of this disorder can be explained by the criticality of *STAT3* for the production of IL-17 by various lymphocytes. IL-17 acts on broadly expressed receptors to increase the production and recruitment of neutrophils to sites of inflammation and is especially important for host defense against *Staphylococcus aureus* and fungal infections (8). It also plays a fundamental role

in a range of autoimmune disorders reflecting broader tissue effector function. STAT3 directly binds many of the key genes required for Th17 differentiation, including the *Il17* gene itself (9, 10). Increasingly, though, it is recognized that Th17 cells are not the only source of IL-17 and that other IL-17-expressing cells can play a key role in controlling bacterial and fungal infections (8).

Although failure to produce IL-17 is an important aspect of the immunopathogenesis of HIES (5, 6), STAT3 also mediates signaling for another cytokine, IL-22, which is important for epithelial barrier function (11). Impaired barrier function in HIES contributes to the atopic dermatitis, staphylococcal skin abscesses, and mucocutaneous candidiasis typical of the disease (12). STAT3 is also important for CD8 T cell memory, so patients with HIES are prone to recurrent *Varicella zoster* and Epstein-Barr virus infections (13). STAT3 has critical functions in B cells because of its role in signaling by IL-6, IL-21, and IL-10, although the precise mechanism underlying the overproduction of IgE is not fully understood. The molecular basis for the craniofacial, skeletal, and vascular abnormalities and the role of STAT3 have yet to be thoroughly dissected.

Treatment of HIES is currently directed toward ameliorating disease manifestations, with limited success. In principle, HCST might be a reasonable therapeutic option for HIES; however, STAT3 has important functions in both hematopoietic and nonhematopoietic epithelial cells, which might limit the efficacy of HSCT. Indeed, recent work in a mouse model of HIES would suggest that HSCT only partially rescues host defense deficits in this model, providing a cautionary note (14).

Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis (CMC) comprises a heterogeneous collection of disorders manifested by recurrent or persistent infections of skin, nails, and mucosa with *Candida* organisms, predominantly *C. albicans*. A recently described genetic lesion underlying CMC is a gain-of-function (GOF) mutation in *STAT1*. As in HIES, the net effect is poor production of IL-17, but in this case a different mechanism is operative. GOF *STAT1* mutations cause exaggerated interferon gamma (IFN- γ) signaling, which inhibits *IL-17* transcription, resulting in susceptibility to fungal infections. Increased IFN- γ signaling may have other relevant functional impacts, and these patients are indeed at risk for autoimmune disease. *STAT1* GOF mutations have also been reported in association with autoimmunity, cerebral aneurysms, squamous cell carcinoma, and IPEX-like (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome with intact regulatory T cells (15). The role of STAT1 and mechanisms underlying these abnormalities are less well defined.

Mycobacterial Infection

Contrasting with CMC is the syndrome caused by loss-of-function *STAT1* mutations, characterized by recurrent mycobacterial infections and disseminated *Bacillus Calmette-Guerin* (BCG). This, too, can be ascribed to the role of STAT1 in IFN- γ signaling. Loss-of-function *STAT1* mutations are dominant negative for type 2 interferon signaling, underlying the patients' susceptibility to mycobacterial infections, but autosomal recessive for type 1 interferon signaling, resulting in normal responses to viral infections (1).

TYK2 associates with the cytoplasmic domains of receptors for several cytokines including type 1 interferon, IL-6, and IL-12. One patient with *TYK2* mutations has been described with a syndrome resembling HIES (16); however, another had a very different phenotype comprising disseminated BCG infection, neurobrucellosis, and cutaneous *Herpes zoster* infection but no atopy

and only mild elevation in IgE levels (17). The distinctive clinical phenotypes presumably relate to the relative importance of TYK2 for different cytokines and potentially different cells.

STAT2 Mutations and Susceptibility to Viral Infection

Only one family with *STAT2* deficiency has been described. One sibling developed disseminated vaccine strain measles following a routine immunization, and a second sibling died of severe disseminated viral infection (18). *STAT2* is required for type 1, but not type 2, interferon signaling (**Figure 2**). IFN- γ primarily activates *STAT1*, creating a *STAT1*–*STAT1* homodimer that localizes to the nucleus to exert downstream effects. Type 1 interferons, by contrast, activate a complex of transcription factors composed of *STAT1*, *STAT2*, and *IRF9*. Deficiency of *STAT2* therefore profoundly affects type 1 interferon signaling but not type 2 IFN- γ signaling, explaining the associated clinical phenotype.

Immunodeficiency and Growth Retardation

Autosomal recessive *STAT5B* mutations cause a complex syndrome characterized by dwarfism, immunodeficiency, and autoimmunity. These clinical abnormalities can be explained by the role of *STAT5* in growth hormone signaling. There are two *STAT5* genes, *STAT5A* and *STAT5B*, and combined deficiency of both genes in mice profoundly affects all hematopoietic cells (19). Deficiency of *STAT5B* alone, however, also impacts immune cells, especially T and NK cells (19). *STAT5B* is important for regulatory T cells and for the key regulatory transcription factor *FOXP3*. This explains the atopy and autoimmunity seen in some cases of *STAT5B* deficiency, including early-onset juvenile idiopathic arthritis, severe eczema, and immune thrombocytopenic purpura—many of which have been linked with functional deficiencies of regulatory T cells (20, 21). Conversely, *STAT5* is also important for T cell memory (22), and thus *STAT5B* mutation can also be associated with recurrent pneumonia and other infections (1). These observations highlight the dual pro- and anti-inflammatory nature of *STAT5*. On one hand, it is involved in development and homeostasis of lymphoid cells, while on the other hand, it limits T cell hyperactivity in conditions of immunocompetency.

THE JAK-STAT PATHWAY AND CANCER

Constitutive activation of JAKs and STATs was first recognized as being associated with malignancy in the 1990s (19). The JAK-STAT pathway can be activated by various mechanisms, including autocrine/paracrine cytokine production, activating mutations of receptors, JAKs or other upstream oncogenes that in turn activate STATs, and activating mutations of STATs themselves.

Polycythemia Vera and *JAK2* Mutations

Polycythemia vera, essential thrombocytosis, and primary myelofibrosis are closely related myeloproliferative diseases (MPDs), all characterized by elevated bone marrow production of erythrocytes and megakaryocytes. Early reports classified each syndrome according to a distinct clinical phenotype, but in the 1950s it was recognized that the three could overlap significantly (23). The genetic basis for this relationship was identified with the discovery of activating mutations of *JAK2*, most commonly V617F, in almost all patients with polycythemia vera and many with essential thrombocytosis and primary myelofibrosis (24). *JAK2* is crucial for signal transduction downstream of the erythropoietin, thrombopoietin, and related receptors that

control erythrocyte and megakaryocyte expansion (1). The V617F mutation lies within the pseudokinase domain, which historically was presumed to be a catalytically inactive negative regulator of JAK2 (25). More recent work, however, has suggested that this domain has catalytic activity responsible for its inhibitory function (25). Elaboration of the pseudokinase domain's crystal structure has created opportunities to develop targeted JAK2 inhibitors for the treatment of MPDs (25, 26). JAK2 can also be targeted for activation: eltrombopag, a small-molecule JAK2 activator, is used to treat refractory aplastic anemia and idiopathic thrombocytopenic purpura (27).

Gain-of-Function Somatic Mutations of JAKs in Cancer

Predating the discovery of the link between *JAK2* mutations and MPDs, somatic activating mutations in JAKs were described in various malignancies (28), although their contribution to disease pathogenesis remains incompletely defined. Somatic *JAK2* mutations have been linked to a number of hematologic malignancies (28, 29), and a cohort study indicated that the V617F mutation was associated with increased mortality in the general population (30). Mutations in *JAK1* have been associated with the development of acute myeloid leukemia, although there is debate surrounding this point (31). *JAK3* mutations have been associated with leukemia and lymphoma (28). Secondary mutations in *JAK3* have been described in juvenile myelomonocytic leukemia and are thought to be associated with disease progression (32).

Aberrant activation of STATs has been found in many tumors. STAT3 is constitutively activated in solid and hematologic cancers (33, 34), and cytokines produced by T cells can activate STAT3 in cancer cells to impact stemness and tumorigenicity (35). STAT3 has also been implicated in the pathogenesis of diffuse large B cell lymphoma (36) and solid-organ malignancies such as breast and nasopharyngeal carcinomas (34). Mutations of the SH2 domain of *STAT3* are present in 40% of large granular leukemias (37). Similar mutations have been identified in ~30% of chronic NK cell lymphoproliferative disorders (38), as well as in the context of aplastic anemia and myelodysplastic syndromes (39, 40). Curiously, some of the mutations seen in large granular leukemia affect the same residues that are altered in HIES—a disease associated with STAT3 loss of function and an increase in the incidence of both T and B cell lymphomas (1). This is notable because *STAT3* mutations typically result in a hypofunctional protein, and it is unclear why patients with HIES have an increased lymphoma risk.

Aberrant STAT5 signaling has also been implicated in the pathogenesis of hematologic and solid-organ malignancies (33, 41). Chronic myeloid leukemia (CML) is characterized by the presence of the BCR-Abl oncogene, resulting in a constitutively active tyrosine kinase (42). CML can be mimicked in mice by forced expression of BCR-Abl. Mice with bone marrow deficient in STAT5, however, are resistant to developing CML, an observation that suggests that STAT5 is essential for the development of CML (42).

Despite the role of STATs in promoting oncogenesis, there is substantial literature that points to a protective role of STATs in cancer. Interferons are critical for the elimination phase of cancer immunoediting, in which the immune system recognizes and destroys transformed malignant cells (43). A subset of human tumors lack the ability to signal through the interferon receptors, including some types of lung cancer, prostate cancer, melanoma, and breast cancer (43, 44). Much of the effect of interferons is mediated by STAT1. Differential STAT1 signaling may influence the clinical phenotype caused by the V617F mutation in *JAK2* (45).

JAKs and STATs and Common, Multigenic Human Diseases

Beyond the identification of monogenic loss- and gain-of-function alleles, an explosion of genome-wide association studies has implicated the JAK-STAT pathway in common human diseases.

Polymorphisms of *STAT1* have been associated with an increased risk of malignancy (46), and polymorphisms of *STAT3* are associated with Crohn's disease and psoriasis (47). *STAT4* single-nucleotide polymorphisms are associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (48); *STAT6* single-nucleotide polymorphisms are associated with asthma and allergy (49). As is the case for most genome-wide association studies, the functional implications of these polymorphisms remain obscure. Nonetheless, a large body of evidence points to fundamental roles for the JAK-STAT pathway in human health and disease, from rare monogenic disorders to more common complex diseases.

THERAPEUTIC TARGETING OF JANUS KINASES

Given the breadth of data implicating JAK-STAT signaling in autoimmune disease and malignancy, it is not surprising that this pathway has become an attractive therapeutic target (**Figure 3**). Although this is an area of intense research, we attempt to summarize recent and impending breakthroughs. We first briefly review the JAK inhibitors (Jakinibs) approved to date by the US Food and Drug Administration (FDA) and then discuss the implications for future work in targeting JAKs and possibly STATs.

Tofacitinib

Tofacitinib was the first selective Jakinib to be tested and later approved in humans. The initial rationale underlying its development was JAK3's essential, nonredundant function in lymphocytes. JAK3 was a particularly attractive therapeutic target because deficiency does not affect nonimmunologic organs or tissues, indicating that the adverse-effect profile of a selective inhibitor could be favorable, at least in terms of nonimmunologic or hematologic toxicity (50, 51). Subsequently, tofacitinib was found to inhibit JAK1 and to a lesser degree JAK2 (52, 53). This broader spectrum targets cytokines and hormones that are important to host defense, development, and homeostasis of hematopoietic and other cells. However, clinical study data thus far available have established that the drug appears to have an acceptable safety profile, sufficient to allow utilization and exploration across a range of immune-mediated diseases, and the ability of tofacitinib to inhibit JAK1 and JAK2 may have improved tofacitinib's efficacy in autoimmunity.

Tofacitinib was effective in preclinical models of several immune-mediated diseases ranging from inflammatory arthritis and transplantation rejection to allergic models (54). A subsequent comprehensive phase II/III clinical trial program demonstrated the acceptable safety and efficacy of tofacitinib in RA (**Supplemental Table 1**; follow the **Supplemental Material** link from the Annual Reviews home page at <http://www.annualreviews.org>). Tofacitinib is effectively used as monotherapy or in conjunction with methotrexate and is effective in distinct patient populations, including those refractory to standard therapy (55–57). Tofacitinib was found to be noninferior to the tumor necrosis factor inhibitor adalimumab, a normal first-choice biologic in the RA paradigm (58). Patients with disease refractory to both conventional and biologic disease-modifying antirheumatic drugs (DMARDs) were responsive to tofacitinib (59), and tofacitinib halted radiographic progression of RA (60, 61). The recently published ORAL-START study reported particularly impressive response rates in methotrexate-naïve patients; in this subset, tofacitinib outperformed methotrexate, a hurdle not previously surpassed in such study designs by other therapies (61).

Clinical trials evaluating tofacitinib have shown promising results in treating several other autoimmune disorders including psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, keratoconjunctivitis sicca, and transplant rejection (62–68). Results were similarly encouraging in


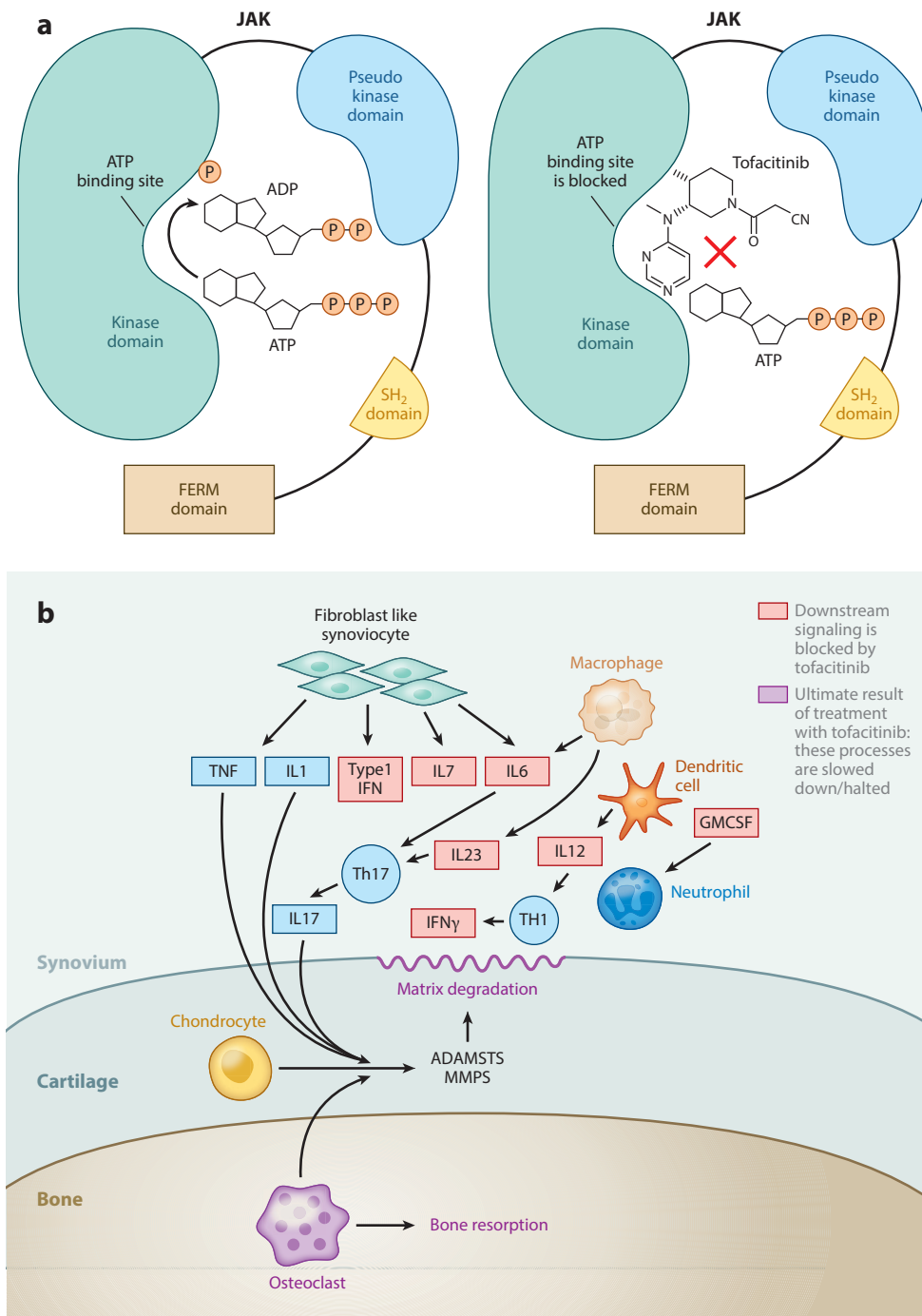
 **Supplemental Material**

Figure 3

(a) Janus kinases contain several domains; the kinase domain is responsible for phosphorylation. This occurs when ATP binds to the ATP-binding site and releases its phosphate, which can then be used to phosphorylate JAKs and cytokine receptors. Tofacitinib competitively inhibits the ATP-binding site and therefore the kinase activity of JAK3. (b) The component cells of the inflamed RA joint are depicted, highlighting key cytokine pathways driving the activation of effector cells and tissue damage. Arrows show a relationship between the cells influenced by these cytokines.



ulcerative colitis (69), but not in Crohn's disease (70).¹ Most recently, topical and oral Jakinibs, including tofacitinib, have shown efficacy in treating immune-mediated alopecia (71, 72).

The efficacy of tofacitinib in RA led to FDA approval in 2012 for patients unresponsive to or intolerant of methotrexate. However, the approval required a "black box" warning and a post-marketing study. Infection rates with tofacitinib have generally been higher than those seen with placebo (55–60, 73, 74). Most infections have been mild upper respiratory infections, urinary tract infections, and episodes of viral gastroenteritis. However, serious and opportunistic infections have also been reported, including *Mycobacterium tuberculosis*, *Cytomegalovirus*, *Pneumocystis jirovecii* pneumonia, and bacterial pneumonias (73, 75–77). Patients treated with tofacitinib seem particularly at risk for infection with *Herpes zoster* relative to patients on other agents (78, 79). There may be a relationship to significant lymphopenia, and serious adverse events occurred with higher frequency in older patients, those with diabetes, and those on higher doses of glucocorticoids. This adverse-event profile is not unexpected because the efficacy of tofacitinib relates directly to the fundamental role of JAKs in immune responses, including response to infection—these complications will need to be carefully evaluated going forward to ensure appropriate patient selection and observation over time. Moreover, new agents targeting JAKs should also be carefully evaluated with this in mind. Encouragingly, recent data from long-term extension studies indicate that risks of adverse events in tofacitinib-treated patients, including most infections, are similar to those seen with other biologic therapies (79, 80).

Cardiovascular events in patients on tofacitinib have been reported (60, 73, 74). Concern regarding cardiovascular disease has largely stemmed from the modest but statistically significant increases in high- and low-density lipoproteins noted in clinical trials. However, the clinical significance of these laboratory abnormalities is not yet clear. Metabolic and immune regulator networks are intertwined, so these observations are not entirely unexpected. Moreover, RA patients treated with tocilizumab, which also causes hypercholesterolemia mediated through its blockade of IL-6R, do not have increased rates of cardiovascular disease as observed thus far, although ongoing outcome studies are evaluating this risk (81).

Another adverse effect of tofacitinib is anemia with neutropenia, usually mild, and presumably related to JAK2 inhibition. Elevations in serum creatinine and transaminases have been noted (77), but consistent effects on renal function are not emerging, although isolated significant problems have been reported.

Malignancies have been associated with tofacitinib, but as with other RA drugs, it has been difficult to establish whether this represents a significant risk (77). In principle, tofacitinib may adversely affect malignancy risk through its effects on JAK1 and JAK2, which are important for interferon signaling and therefore for cancer immunoediting (43). Given the relatively small number of malignancies reported, further studies will be needed to clarify risk and relationship to duration of therapy.

Ruxolitinib

A potent inhibitor of JAK1 and JAK2, ruxolitinib was the first FDA-approved Jakinib. It was approved for the treatment of intermediate- and high-risk primary myelofibrosis after the COMFORT-I and COMFORT-II trials demonstrated marked responses to therapy. Efficacy was irrespective of the presence of JAK2V617F mutations (53). Ruxolitinib has also been studied

¹Ongoing clinical trial: <http://clinicaltrials.gov/ct2/show/NCT01786668?term=&tofacitinib&rank=9>, <http://clinicaltrials.gov/ct2/show/NCT01500551?term=&tofacitinib&rank=28>.

in psoriasis and in RA, where preliminary results have been encouraging (53). Further studies are ongoing for the treatment of polycythemia vera, essential thrombocytosis, a variety of malignancies, and alopecia areata.²

Oclacitinib

Oclacitinib is a pan-JAK inhibitor recently approved for the treatment of atopic dermatitis in canines (82). Although it is not currently being studied in humans, its effectiveness in treating allergic skin disease illustrates the breadth of anti-inflammatory effects that can be seen with Jakinibs and provides a rationale for the evaluation of this class of drugs in immune-mediated dermatologic conditions.³

Second-Generation Jakinibs and the Future of Targeting JAKs

At present, 25 Jakinibs are currently being tested in various conditions, including asthma, malignancies and myeloproliferative diseases, and a host of autoimmune conditions (**Table 2**). The first FDA-approved Jakinibs inhibit multiple JAKs and consequently inhibit a relatively broad spectrum of cytokines. This is also true for other Jakinibs in clinical trials. Baricitinib, a JAK1/JAK2 inhibitor, has shown promising results in the treatment of RA (51); phase II trials are also ongoing for RA and psoriasis and in the treatment of autoinflammatory diseases.⁴ The JAK1/2 inhibitor momelotinib has shown encouraging results in the treatment of myelofibrosis (83); a phase III trial is ongoing.⁵ The ability to inhibit multiple cytokines has implications for efficacy and adverse-effect profiles that can be traced directly to the mechanism of action. Via JAK1 and JAK2 targeting, these agents can inhibit all cytokine receptors containing the γ c chain, the β common chain (β c, used by IL-3, IL-5 and granulocyte-macrophage colony stimulating factor), and gp130 (used by IL-6 family cytokines), as well as interferons, interleukins (IL-12, IL-23, IL-27), and the hormone-like cytokines (**Figure 2**). Many of these cytokines are inhibited to various degrees, due to relative selectivity and pharmacokinetics, giving these medications an acceptable therapeutic index. However, the goal of more selectively targeting a single JAK remains attractive, especially in the setting of long-term use for autoimmune disease.

Phase II trials have demonstrated efficacy of the JAK3 inhibitor VX-509 (84) and the JAK1 inhibitor GLPG0634 (85, 86) in treating RA. It must be acknowledged that even many of these second-generation inhibitors are not entirely specific to one JAK and that larger confirmatory studies will be required as this class of medicines continues to expand.

Another crucial question for clinical use relates to the optimal dosing regimens and utility in various phases of different diseases. Thus, although tofacitinib has been evaluated in comparison with DMARDs, it may be more effective as an induction regimen in acute immune-mediated disease, in place of steroids or even cyclophosphamide. As with steroids, flexible dosing regimens

²Ongoing clinical trials: <http://clinicaltrials.gov/ct2/show/NCT01751425?term=ruxolitinib&rank=1>, <http://clinicaltrials.gov/ct2/show/NCT02119676?term=ruxolitinib&rank=6>, <http://clinicaltrials.gov/ct2/show/NCT00726232?term=ruxolitinib&rank=11>, <http://clinicaltrials.gov/ct2/show/NCT01950780?term=ruxolitinib+alopecia&rank=1>.

³Ongoing clinical trial: <http://clinicaltrials.gov/ct2/show/NCT02001181?term=tofacitinib+dermatitis&rank=1>.

⁴Ongoing clinical trials: <http://clinicaltrials.gov/ct2/show/NCT01710358?term=baricitinib&rank=12>, <http://clinicaltrials.gov/ct2/show/NCT01724580?term=baricitinib&rank=16>, <http://clinicaltrials.gov/ct2/show/NCT01490632?term=LY3009104+psoriasis&rank=1>.

⁵Ongoing clinical trial: <http://clinicaltrials.gov/ct2/show/NCT01969838?term=momelotinib+myelofibrosis&rank=2>.

Table 2 Jakinibs and STAT inhibitors

Drug	Target	Status	Diseases
Ruxolitinib (INC424)	JAK1, JAK2	<i>FDA approved</i> Phase II Phase 2b	Polycythemia, myelofibrosis Various cancers Psoriasis (topical)
Tofacitinib	JAK3>JAK1»(JAK2)	<i>FDA approved</i> Phase III Phase II	RA Psoriasis, ulcerative colitis Spondyloarthropathy, JIA Transplant rejection
Oclacitinib	JAK1	<i>FDA approved</i>	Canine allergic dermatitis
Baricitinib	JAK1, JAK2	Phase II	RA, psoriasis, diabetic nephropathy, autoinflammatory disease
Momelitinib	JAK1, JAK2	Phase III	Myelofibrosis
GLPG0634	JAK1	Phase II	RA, Crohn's disease
INCB047986	JAK inhibitor	Phase I	Lymphoma, solid tumors
INCB039110	JAK1, JAK2	Phase II	Psoriasis, RA
CYT387	JAK1, JAK2	Phase II	Myelofibrosis
ASP015K	JAK1>JAK3»JAK2	Phase II	Psoriasis, RA
R333	JAK/SYK	Phase II	Discoid lupus (topical)
PF-04965842	JAK1	Phase I	Healthy adults
GLG0778	JAK1	Phase II	SLE
GSK2586184	JAK1	Phase II	SLE, psoriasis
VX-509	JAK3	Phase IIb	RA
Lestaurtinib	FLT3, JAK2, TRKs	Phase II	AML, PV/ET, myelofibrosis
Pacritinib	JAK2	Phase II	Myelofibrosis, myeloid leukemias, MDS
LY2784544	JAK2	Phase II Phase I	Myelofibrosis, various cancers
AZD1480	JAK1, JAK2	Phase I	Myeloproliferative diseases, various cancers
XL019	JAK2	Phase I, terminated	Myelofibrosis, PV
BMS-911543	JAK2	Phase II	Myelofibrosis
NS-108	JAK2, SRC	Phase II	Myelofibrosis
PF-06263276	pan-JAK	Phase I	Healthy adults (topical)
SV1578	JAK2, Flt3	Phase I	Healthy adults
ISIS-STAT3Rx (AZD9150)	STAT3	Phase II	Various cancers
OPB-51602	STAT3	Phase I	Nasopharyngeal carcinoma
OPB-31121	STAT3	Phase I	Various cancers

Abbreviations: AML, acute myeloid leukemia; ET, essential thrombocytosis; JIA, juvenile idiopathic arthritis; PV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

with dose tapering may have utility. Moreover, the development of topical formulations has implications for dermatologic and pulmonary disease. Thus, it may take time to fully appreciate the optimal ways in which these drugs can be used to treat the broad range of clinical scenarios for which they are being evaluated. They may also offer utility for tissue repair, establishing immune tolerance and facilitating stratification by virtue of accessible biomarker profiles.

THE PROSPECT OF STAT INHIBITORS

Because STATs are also key nodes in signal transduction and are frequently activated in the setting of malignancy, considerable effort has been expended for more than two decades to develop STAT inhibitors. This effort has met with limited success due to issues with bioavailability, in vivo efficacy, and selectivity. Conceptually, rational targeting of STATs may be achieved by blocking phosphorylation, disrupting the SH2 domains that mediate binding to phosphorylated receptors and dimerization, or interfering with DNA binding. It is the last of these methods that led to the development of the first STAT inhibitors appropriate for clinical use. Oligonucleotide-based STAT inhibitors are currently being tested in the treatment of various malignancies (**Table 2**). Clinical trials for advanced malignancies are also under way for an even newer group of small-molecule inhibitors targeting STAT3, including OPB-51062 and OPB-31121.⁶ Preclinical results indicate that STAT inhibitors are effective in animal models of autoimmune disease (87). Intrabodies, which bind with great specificity to phosphorylated STAT3 (88), represent a possible novel avenue for the development of STAT inhibitors.

The homology of STAT3 with other STATs, especially STAT1, presents a singular challenge in the design of STAT inhibitors. STAT1 mediates interferon signaling and is critical for apoptosis, cell death, and defense against pathogens; a safe and effective STAT3 inhibitor would presumably have minimal activity against STAT1. STAT3 also has important diverse roles in barrier function and host defense, as well as inhibiting tumorigenesis; these factors will need to be considered in clinical trials of STAT inhibitors.

Empiric targeting of STATs is another strategy that has been employed, and a variety of drugs have been “repurposed” as STAT inhibitors. These include lisofylline, fludarabine, pimizide, sulforaphane, pyrimethamine, and the nutraceutical curcumin. The precise molecular and structural basis through which they interfere with STAT action is incompletely understood.

CONCLUSIONS

The discovery of the JAK-STAT pathway and its role in health and disease represents one of the most exciting developments in modern medicine and now serves as a paradigm for cell signaling and translational science. Basic molecular strategies together with genetic and phenotypic analysis have led to better immunopathogenic insights, diagnostic advances, and new therapeutic options for both rare and common diseases. Clearly, many challenges remain in elucidating how this evolutionarily conserved pathway regulates chromatin biology and cellular differentiation. Furthermore, much work remains in dissecting the precise mechanisms by which Jakinibs exert their effects vis-à-vis the various cytokines that are inhibited in different clinical scenarios. The second-generation selective Jakinibs also need to be investigated further to determine whether they represent an advance over existing drugs. It will be exciting to see how the story unfolds over the next few years, as we learn how to use these and other inhibitors of the JAK-STAT pathway.

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⁶Ongoing clinical trials: <http://clinicaltrials.gov/ct2/show/NCT02058017?term=stat3&rank=4>, <http://clinicaltrials.gov/ct2/show/NCT01406574?term=OPB-31121&rank=4>.

Pfizer, as well as honoraria from Eli Lilly and Galapagos, in connection with development of kinase inhibitors.

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