Invited Review

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STAT1/STAT3 Gain of Function and Mechanisms of Immune Dysregulation

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Abstract

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathways are essential for maintaining prompt immune responses to various cytokines. Both loss- and gain-of-function mutations in the JAK and STAT molecules result in different disease profiles in inborn errors of immunity. The discovery of gain-of-function mutations in STAT1 and STAT3 expanded immunological investigations aimed at understanding both signaling pathways and their associated disorders. Both defects are distinct from loss-of-function mutations that lead to alterations in immune regulation. In this context, we wanted to take a look at both diseases and focus on the mechanisms.

Keywords: Janus tyrosine kinase, signal transducer and activator of transcription, gain of function, immune dysregulation, autoimmunity

JAK-STAT Pathway

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathway is one of the most important examples of signal transduction from the cell membrane to the nucleus. Many cytokines, hormones, and growth factors use the JAK-STAT signaling pathway to initiate cellular responses. This particular pathway consists of JAK and STAT molecules (1). Briefly, binding of a cytokine to the corresponding receptor activates JAKs (a tyrosine kinase), which then phosphorylate themselves and the bound receptors to recruit inactive STAT monomers. After binding, the STATs are phosphorylated and dimerized. The dimeric STATs then go to the nucleus, where they bind specific DNA sequences and activate gene transcription (2).

There are four JAKs [JAK1, JAK2, JAK3, tyrosine kinase 2 (TYK2)] and seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6) responsible for various cytokine signaling (3). The importance of JAKs and STATs has increased with the discovery of new genes involved in inborn errors of immunity (4). The delicate balance of these molecules is much more pronounced in regulating immune deficiency and excessive immune response that occurs in various diseases. Pathogenic variants can cause loss-of-function (LOF), gain-of-function (GOF), dominant-negative function (DN), or haploinsufficiency (HI) of the encoded gene (5). To date, LOF and GOF variants have been described in STAT1, STAT2, STAT3, STAT5B (6), and more recently in STAT6 (7-10).

STAT1 Gain of Function Disease

STAT1 is the first STAT identified in the biological system and is involved in type I [interferon (IFN)-α, IFN-β], type II (IFN-γ), type III (IFN-λ) interferons, and interleukin (IL)-27 signaling pathways (4,11). Following viral infection, IFN-α and IFN-β bind to their receptor (IFNR), activating JAK1 and TYK2 (5). JAK1 and TYK2 then lead to the formation of STAT1/STAT2 heterodimers. The binding of these heterodimers to Interferon regulatory factor 9 (IRF9, also previously known as p48) leads to the forming of the IFN-stimulated genes (ISG)-3 complex. Subsequently, The ISG-3 complex migrates to the nucleus, binds the type I interferon-stimulated response element, and activates gene transcription (12). On the other hand,

STAT1 homodimers form the IFN-γ-activated factor (GAF) complex, which binds to IFN-γ activated sequences (GAS) involved in the up-or down-regulation of ISGs and IFN-regulated genes (IRGs) (Figure 1A). After activation, tightly regulated proteins like protein tyrosine phosphatases and suppressors of cytokine signaling (SOCS) repress the activity of the JAK-STAT pathway (13).

STAT1 GOF mutations result in an exaggerated STAT1 response upon stimulation with IFN-α, IFN-β, IFN-γ, or IL-27 due to hyperphosphorylation of STAT1 or delayed STAT1 dephosphorylation (10,13). In addition to the overtranscription of STAT1-inducible genes, the generation of IL-17-producing T-cells via STAT1 is also impaired. Expression of PD-L1 on naïve T-cells requires IL -27, and overexpression of PD-L1 could impair the differentiation of naïve T-cells into Th17 cells (Figure 1B). Another possible explanation could be the deficient function of STAT3 due to abnormal activation of STAT1 in response to IL-6, IL-21, and IL-23 (14).

The genetic mutations have been described in the DNA binding domain (DBD), coiled-coil domain (CCD), linker domain, and SH2 domain (15).

While certain mechanism is related to hyperphosphorylation or delayed dephosphorylation, previous studies suggest that premature nuclear import with normal phosphorylation/dephosphorylation rate, increased nuclear accumulation, decreased mobility, or immobility in the nucleus leads to STAT1 hyperactivation (16).

Chronic mucocutaneous candidiasis (CMC) is one of the major symptoms in patients with STAT1 GOF mutation, and the lifetime risk of CMC is almost 100% (15). In addition to CMC, other bacterial and viral infections may also occur (Table 1). Patients may experience recurrent/severe upper and lower respiratory tract infections (URTI and LRTI, respectively), leading to bronchiectasis. Mycobacterial infections may also be among the infectious agents (17,18). Impaired response to IFN-γ is thought to be responsible for mycobacterial susceptibility (17,18). Autoimmune and autoinflammatory diseases may occur in nearly 40% of patients. Deficient quantitative and qualitative humoral immunodeficiencies have been reported. The inadequate B-cell response may be due to impaired IL-21 dependent STAT3 signaling (19).

Patients may present with an immune dysregulation-polyendocrinopathy- enteropathy X-linked (IPEX)-like syndrome that includes type 1 diabetes, autoimmune thyroiditis, and immune cytopenia despite normal Treg cell numbers and function (20). Interestingly, no autoantibodies to IFN-α, IL-17, and IL-22 were found. Almost one-third of patients have autoimmune features (Table 1), and the reason for the autoimmunity remains to be elucidated. One hypothesis is that increased IFN-α levels may cause autoimmunity, as has been observed in patients receiving IFN-α therapy (20,21). It has also been reported that gene transcription is increased in interferon-stimulated genes (22). Despite normal Treg cell numbers and function, secretion of the anti-inflammatory IL-10 and production of induced Treg cells may be impaired, similar to STAT5b deficiency (23). Impaired differentiation of circulating T follicular helper (Tfh) cells has been demonstrated

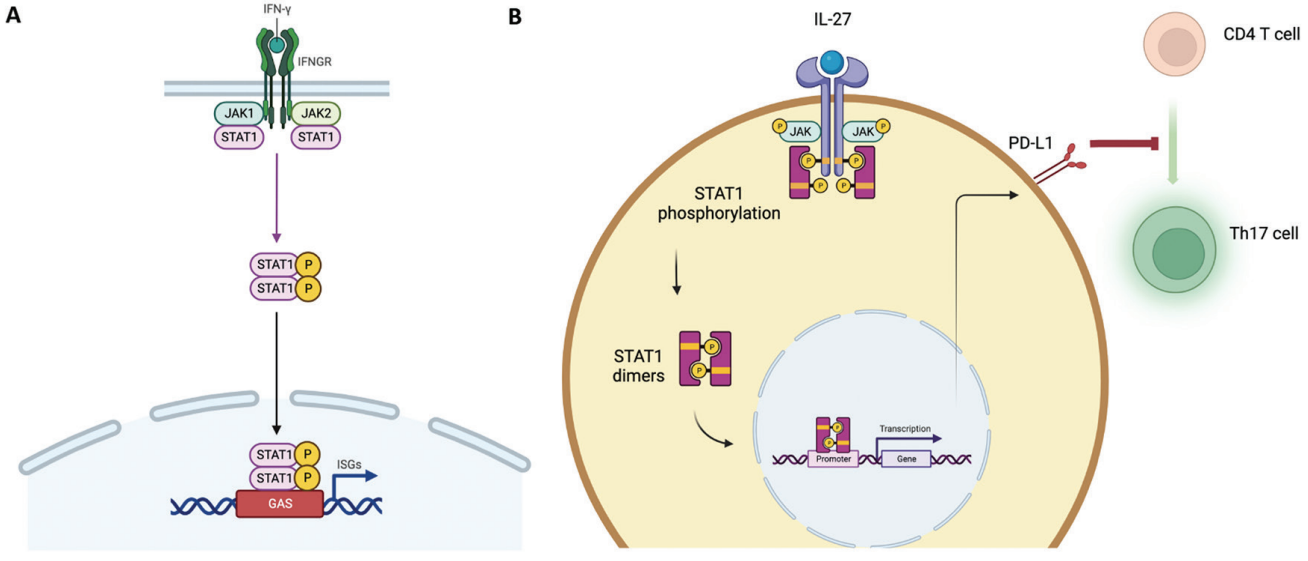

Figure 1. JAK-STAT1 pathways and related immune mechanism of low Th17 cells. (A) STAT1 homodimeric structure forms the IFN-γ-activated factor (GAF) complex, which binds to IFN-γ-activated sequences (GAS) involved in the up-or down-regulation of interferon-stimulated genes. (B) Defective differentiation of naïve T-cells to Th17 cells due to increased PD-L1 expression in STAT1 GOF patients. Created with BioRender.com.
STAT: Signal transducer and activator of transcription, GOF: Gain-of-function, IFN: Interferon

in STAT1 GOF patients, similar to STAT3 LOF, IL-10 LOF, and IL21R LOF patients. In addition to impaired humoral immune responses, these abnormal Tfh subsets may cause increased IFN-γ signaling responsible for autoimmunity and autoinflammation (24). It has also been hypothesized that although Treg cell numbers and functions are preserved, overactivation of STAT1 may cause Tregs to differentiate into Th1-like cells, resulting in functional IL-10 deficiency (23). These patients also tend to develop vascular abnormalities such as aneurysms, particularly in the cerebral vasculature and are susceptible to multiple diseases (19). Malignancies have been reported in patients with esophageal candidiasis, particularly squamous cell carcinoma (21).

The immunologic phenotype may include low $CD4^+$ and $CD8^+$ T-cells, low B-cells, low memory B-cells, low NK cells, and reduced NK cell cytotoxicity. Immunoglobulin concentrations may be normal, reduced, or increased, and poor antibody response has also been described in the patients (21). Intrinsic B-cell defects may contribute to poor antibody responses. Naive B cells from patients with STAT1 GOF mutation respond poorly to IL-21, which plays a central role in B-cell differentiation, isotype switching, and affinity maturation (25). Increased apoptosis of B-cells was also noted by Romberg et al. (14). The reason for the decreased NK cell functions is thought to be STAT1-induced SOCS1-mediated suppression of STAT5, which is involved in terminal NK cell differentiation and NK cell toxicity, as has also been observed with STAT3 GOF mutations (26). Thus, NK cell dysfunction could contribute to the susceptibility to viral infection observed in patients with STAT1 GOF mutations. Another possibility is that increased PD-L1 expression impairs $CD4^+$ and $CD8^+$ T-cells against viruses (27).

The leading causes of death are severe infections (38%), cancer (24%), and cerebral hemorrhage due to aneurysms (15%) (28). These are also risk factors for poor outcomes. Most patients require antifungal treatment because of CMC and invasive fungal infections. Antibacterial prophylaxis and immunoglobulin replacement therapies are also commonly used to prevent bacterial infections. Immunosuppressive treatment may be required to control non-infectious manifestations (19). Hematopoietic stem cell transplantation (HSCT) has been performed in several patients with poor control of infections and autoimmune manifestations (17,29). Although it has been proposed as a curable treatment option, graft failure and transplant-related mortality have been reported after transplantation, probably in association with augmented IFN responses, which could be controlled by using JAK inhibitors as a bridge therapy (26).

Table 1. Clinical features in STAT1 GOF mutations

	Clinical features	Mechanism
Infections	**Bacterial** *Staphylococcus aureus, Streptococcus* spp., *Pseudomonas aeruginosa*, *Haemophilus Influenzae*	• Impaired Tfh differentiation • Defective IL-21 response • Increased B-cell apoptosis
	Viral Herpes simplex virus, Varicella zoster virus, *Cytomegalovirus,* Epstein-Barr virus	• Defective NK cell differentiation and NK cell toxicity • Increased PD-L1 expression
	Fungal *Candida albicans, Cryptococcus* spp., *Pneumocystis jirovecii, Aspergillus* spp., *Penicillium marneffei (invasive), Mucormycosis, Coccidioidomycosis, and Histoplasmosis*	• Defective development of Th17 cells (impaired IL-17A, IL-17F and IL-22 signaling) due to increased Th17 suppressors (IFN-α/β, IFN-γ, and IL-27) • Over expression of PD-L1 may impair the differentiation of naïve T-cells to Th17 cells • Decreased functioning of STAT3 secondary to abnormal STAT1 activation
	Mycobacterial Tuberculous (*Mycobacterium tuberculosis*) or non-tuberculous (*Mycobacterium avium,* BCG vaccine etc.)	• Impaired IFN-II related immune response
Autoimmunity and autoinflammation	Cytopenia, hypothyroidism, type 1 DM, vitiligo, alopecia, psoriasis, systemic lupus erythematosus Crohn disease, ulcerative colitis	• Increased transcription of interferon stimulated genes • Functional IL-10 deficiency • Abnormal Tfh cell subsets and functions
Malignancies	Squamous cell carcinoma (on CMC basis), papillary thyroid cancer, melanoma, lymphoma, leukemia, prostate cancer	• Defective NK cells due to impaired STAT5 signaling
Other	Aneurysms Enamel defect Delayed dental shedding	• The plausible mechanism for aneurysm susceptibility could be mycotic translocation

STAT: Signal transducer and activator of transcription, GOF: Gain-of-function, IL: Interleukin, IFN: Interferon, CMC: Chronic mucocutaneous candidiasis, NK: Natural killer, BCG: Bacillus Calmette-Guérin

Among the JAK inhibitors, ruxolitinib has been used as a treatment modality to cure CMC and autoimmune manifestations. Ruxolitinib has been shown to reverse STAT1 hyperactivation by suppressing ligand binding, thereby improving Th1 and Tfh responses (30,31). However, exacerbation of fungal infections has also been reported in one patient as a treatment failure (30). Recently, ruxolitinib has been successfully administered as bridging therapy before HSCT to control disease (26).

STAT3 Gain of Function Disease

Activating germline mutations in STAT3 were first described by Flanagan et al. (32) in patients with early-onset autoimmunity. In later publications, the clinical phenotype was expanded to include IPEX-like disease as in the first article (32), autoimmune lymphoproliferative syndrome (ALPS), and STAT5b deficiency-like phenotype (Table 2) (33,34). The most pronounced manifestations were autoimmune cytopenia, lymphoproliferation, short stature, interstitial lung disease, and recurrent infections (32-34). Decreases in switched memory B-cells, NK cells, dendritic and plasmacytoid cells, and hypogammaglobulinemia were noted in the majority of patients (33,34). Hyperactivation of STAT3 has not been shown to be related to either cytokine-induced hyperphosphorylation or delayed dephosphorylation, but rather, it is thought to be an intrinsic defect (33,34). Furthermore, the imbalanced STAT3/STAT5 signaling decreases phospho-STAT5, reducing Treg cells. The diminished Tregs is also attributed to increased IL-6 signaling (33).

With the advance of high throughput DNA sequencing, many disorders come to the scan caused by different mutations leading to opposite functions in the same molecule. In contrast to STAT3-GOF, dominant-negative STAT3 mutations cause Hiper-IgE syndrome (AD-HIES). The clinical manifestations of AD-HIES include immunologic (i.e., recurrent bacterial and fungal infections, formation of cold abscesses) and non-immunologic (connective tissue abnormalities) features (35). Interestingly, most of our findings on the functions of STAT3 come from extensive investigations of different cytokine responses in patients' cells that helped elucidate the proper intracellular STAT3 signaling. On the other hand, somatic activating STAT3 mutations have been associated with T-cell and NK-cell large granular cell leukemia (36).

Table 2. Consequences of STAT3 hyperactivation

IPEX syndrome-like features	• Early onset autoimmunity • Eczema • Enteropathy
ALPS-like features	• Autoimmune cytopenia • Lymphoproliferation (hepatosplenomegaly, lymphadenopathy)
STAT5b deficiency like features	• Postnatal growth failure • Short stature • Lymphocytic interstitial lung disease
Recurrent infections	• Bacterial, viral, fungal, opportunistic and mycobacterial

STAT: Signal transducer and activator of transcription, ALPS: Autoimmune lymphoproliferative syndrome

STAT3 is a transcription factor involved in various cytokine signaling, including interferons, IL-2, IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27. STAT3 plays a central role in cell survival, proliferation, and differentiation. Upon binding of cytokines to their receptors, JAKs are activated, which in turn phosphorylate STAT3, leading to its migration to the nucleus, where it further binds to DNA sequences (37). Unlike STAT1 GOF, hyperphosphorylation of STAT3 was not detected even after cytokine stimulation. Therefore, it is also difficult for patients carrying STAT3 variants to be determined as GOF. It is more likely that GOF variants cause a prolonged activation state (37). In some patients, increased DNA binding and nuclear retention have been suggested as mechanisms (38).

In search of the underlying mechanisms leading to the clinical phenotype, SOCS3 has been shown to play a critical role in regulating other STATs. Hyperactivation of STAT3 leads to increased SOCS3 activity, which acts as a negative regulator of the other STAT molecules, such as STAT5, involved in growth hormone signaling (38). After stimulating STAT3 GOF molecules, an increase in IL-10 and BCL-3 and a decrease in CXCL8 were demonstrated. It was hypothesized that increased expression of pro-survival genes might contribute to a defect in apoptosis responsible for the ALPS-like phenotype (39). Therefore, increased double-negative T-cells (DNT) observed in patients with lymphoproliferation and autoimmune cytopenia may support this hypothesis.

In addition to its role in the downstream pathway of growth hormone, STAT5 is also important for Treg differentiation and functions. Decreased Treg levels have been demonstrated in many STAT3 GOF patients (33,34). The reason for autoimmunity was associated with defective Tregs in some patients, although there were also patients with normal Treg number and function with autoimmune features (33,34).

STAT3 plays an important role in B-cell functions. IL-10 and IL-21 as STAT3-activating cytokines are potent B-cell activators and are involved in B-cell proliferation, class switching, and differentiation (40). Both cytokines have been found to be impaired in STAT3 LOF patients (40). Conversely, increased B-cell activity was not detected in STAT3 GOF patients. Patients generally exhibit hypogammaglobulinemia and decreased numbers of switch memory B-cells. As for antibody-mediated autoimmunity in these patients, B-cell tolerance appears to be impaired (32,34).

A genotype-phenotype correlation was not demonstrated, although some phenotypes were clustered in some domains. Endocrinopathies were more pronounced in the SH2, CCD, and DBD domains, whereas lymphoproliferative disorders were more common in the CCD and N-terminal domain variants. Patients with N-terminal domain variants were found to have better survival than patients with SH2 domain variants, who had the poorest survival (41).

Immunosuppressive treatment is the mainstay of therapy with respect to the state of immune dysregulation seen in most patients. In addition to steroids, sirolimus, mycophenolate mofetil, and rituximab have been used with partial success. Antibacterial prophylaxis and immunoglobulin substitution may be useful to prevent infectious complications (37,41). Given the hyperactivated state of the disease, control of upstream signals seems logical. Jakinibs have been used in many patients who were already unresponsive to conventional immunosuppressants. Ruxolitinib and tofacitinib were able to reverse autoimmune complications such as enteropathy, autoimmune cytopenia, and interstitial lung disease in many patients (30,42,43). IL-6 blockade was particularly successful in arthritis and interstitial lung disease in combination with Jakinibs (33). HSCT may be a therapeutic option in cases refractory to immunosuppressants and with poor disease control. Very few data on HSCT have been published, showing a survival rate of almost 62% (41).

Finally, there are still unanswered questions about immune system dysregulation in STAT1 and STAT3 GOF mutations. However, we know that GOF is not always the opposite of LOF, as summarized in this review. Further studies are needed to explore these intriguing puzzles.

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