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The Ying and Yang of STAT3 in Human Disease

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Abstract

The transcription factor signal transducer and activator of transcription 3 (STAT3) is a critical regulator of multiple, diverse cellular processes. Heterozygous, germline, loss-of-function mutations in *STAT3* lead to the primary immune deficiency Hyper-IgE syndrome. Heterozygous, somatic, gain-of-function mutations in *STAT3* have been reported in malignancy. Recently, germline, heterozygous mutations in *STAT3* that confer a gain-of-function have been discovered and result in early-onset, multi-organ autoimmunity. This review summarizes what is known about the role of STAT3 in human disease.

Keywords

STAT3; Hyper-IgE syndrome; Job syndrome; monogenic autoimmunity; gain-of-function

INTRODUCTION

Since its initial discovery in 1994 [1], signal transducer and activator of transcription 3 (STAT3) has been recognized as a transcription factor critical for numerous essential and very diverse cellular processes [2]. The focus of this brief review is the role of STAT3 in the setting of human disease as has been revealed by patients discovered to have mutations in *STAT3* as the genetic basis for immunodeficiency, malignancy and autoimmunity [3–8]. An understanding of this pleiotropic molecule is required for appreciation of the phenotypes of these rare disorders.

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STAT3

STAT3 belongs to a 7-member family of transcription factors (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) responsible for transmitting diverse cytokine signals from the cellular membrane to the nucleus to alter gene expression [9]. *STAT3* is composed of 24 exons located on chromosome 17q21, and STAT3 is highly conserved across species, with only one amino acid difference between mouse and human [10, 11]. The major isoform of human STAT3, STAT3 α , is a 770 amino acid, 92kDa protein containing 6 domains (Figure 1) [12]. The STAT3 β isoform is formed by use of an alternative splice acceptor site in exon 23, leading to replacement of the terminal 55 amino acids of STAT3 α with a 7 amino acid sequence unique to STAT3 β [13, 14]. STAT3 β activation results in distinct gene expression profiles [12, 15]; less is known about the other STAT3 isoforms [16, 17].

In the classic STAT signaling pathway, after a cytokine binds to its receptor, one of 4 receptor associated kinases of the Janus kinase (JAK) family (JAK1, JAK2, JAK3 or Tyk2) becomes activated and phosphorylates the cytokine receptor, leading to recruitment of STAT molecules to the activated receptor [9]. Receptor-associated STAT molecules are then phosphorylated on a tyrosine residue in the transactivation domain, allowing them to dimerize, and subsequently translocate to the nucleus to alter gene expression [9]. Despite recognition of this fundamental pathway, the exact manner in which more than 60 cytokines are able to exert unique cellular effects using combinations of only 4 JAKs and 7 STATs is still an area of active investigation [18].

Activation of STAT3 has been demonstrated downstream of numerous cytokines through multiple receptor types including the gp130 family of cytokine receptors (such as IL-6, the classic activator of STAT3), γ chain cytokine receptors, type I and II interferon receptors, the IL-10 family receptors, the IL-12 and IL-23 family receptors as well as receptor tyrosine kinases like the epidermal growth factor receptor [18, 19]. After activation and translocation to the nucleus, STAT3 classically binds the canonical sequence CCT(N)₃GAA to activate or repress gene transcription [20]. Some specificity of the activation of STAT3 downstream of multiple stimuli is likely imparted through cell type-specific features; however, growing evidence suggests additional specificity results from non-classical functions of STAT3.

Potential non-classical roles for STAT3 have recently been thoroughly reviewed [18]. They include binding to non-canonical motifs, induction of non-coding transcripts or micro RNAs, neutral binding without transcript induction, formation of higher ordered signaling complexes, such as STAT tetramers, which may participate in multi-protein, enhancer-binding complexes, and contributions to epigenetic remodeling. Additional roles for unphosphorylated STAT3, as well as contributions of serine phosphorylation at residue 727 and other post-translational modifications such as acetylation are also recognized [18, 21, 22]. Further specificity is likely provided by variation in the intensity and duration of cytokine stimuli, as STAT3 is known to shuttle back to the cytoplasm after dephosphorylation in the nucleus [18]. STAT3 activation is also negatively regulated by several separate mechanisms including upregulation of suppressor of cytokine signaling 3 (SOCS3) and protein inhibitor of activated STAT3 (PIAS3) [23]. Another layer of

complexity may be due to the activity of STAT3 in non-classical cellular compartments such as the mitochondria [24].

Roles of STAT3 Revealed by Murine Models

Cytokine activation of STAT3 ultimately leads to many complex, and at times contradictory, pathways including proliferation, differentiation, migration, inflammation and apoptosis [25]. The importance of STAT3 was clearly revealed by the finding that germline deletion of *STAT3* in mice results in an early embryonic lethality [26]; the only STAT molecule which is embryonic lethal.

Cell-specific knock-out mice have furthered the understanding of STAT3 within the hematopoietic system, in particular demonstrating the role for STAT3 in CD4⁺ T cell differentiation. STAT3 plays a critical part in the development of IL-17 producing CD4⁺ T cells (Th17 cells) by regulating transcription of the genes encoding IL-17A, IL-17F and the Th17 lineage transcription factors ROR γ t and ROR α [27]. STAT3 can simultaneously inhibit the development of induced CD4⁺ T regulatory cells (iTregs) by inhibiting their lineage specific transcription factor FOXP3 [28]. An additional role for STAT3 in the formation of T follicular helper (Tfh) cells has also been shown, with impaired B cell differentiation and humoral immunity in the absence of STAT3 in Tfh cells [28].

Conditional deletion of *STAT3* from B cells, CD8⁺ T cells, macrophages/ neutrophils and natural killer (NK) cells has also shown a role for STAT3 in T cell-dependent antibody production, memory T cell development, regulation of granulocytes (through IL-10 signaling) and inhibition of NK cell anti-tumor responses [27–32]. Studies in cells from humans with impaired, but not absent, STAT3 function generally support these conclusions from mouse models, as described here.

GERMLINE *STAT3* LOSS-OF-FUNCTION: HYPER-IGE SYNDROME

History

The triad of eczematoid dermatitis with recurrent skin and pulmonary infections that we now recognize to be autosomal dominant Hyper-IgE syndrome (AD-HIES) was first described as Job's syndrome in 1966, in reference to the biblical character afflicted with cutaneous boils [33]. The recognition of highly elevated levels of IgE in these patients followed in 1972 [34]. A more contemporary representation of the triad of AD-HIES is: eczematoid dermatitis, recurrent skin and sinopulmonary infections with highly elevated IgE. It was not until 2007 that germline, dominant-negative, heterozygous mutations in *STAT3* causing a loss-of-function were discovered to be the genetic basis of AD-HIES [3, 4].

Clinical Features

The incidence of AD-HIES has been estimated at 1:100,000 with no gender bias [10, 35]. The presenting symptom in most patients is a neonatal rash [36], but patients are regularly diagnosed in adulthood. The mean age of diagnosis in one large cohort was 6.8 years with a range of 0–50 years [36]; survival to age 50 years was 93% in this cohort.

The major features of AD-HIES (representing 214 patients in 5 large cohorts) are represented in Table 1 along with their incidence [35–39]. Virtually every patient experiences eczematoid dermatitis, with skin infections. These are typically caused by *Staphylococcus aureus* and are classically non-inflammatory “cold” abscesses. Most patients also have recurrent (>3 lifetime episodes) pneumonia, most often caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*. This can lead to the development of chronic lung disease with pneumatoceles and bronchiectasis and increased risk of *Aspergillus* and *Pseudomonas* pneumonias [36]. One of the more defining infectious features of AD-HIES is chronic mucocutaneous candidiasis (CMC), usually from *Candida albicans*. Patients with AD-HIES are also recognized to have impaired control of chronic herpes viruses [40]. The bacterial infections experienced in AD-HIES can be severe, but, like the *Candida* infections, are largely restricted to mucosal surfaces.

Most AD-HIES patients develop a characteristic facies with age, including increased interalar distance, prominent forehead and coarse skin. Other features frequently reported in association with AD-HIES include retained deciduous teeth, scoliosis, joint hyperextensibility, vascular malformations [41] and increased non-traumatic fractures. Non-immune features are included in Table 1. There also seems to be an increased incidence of lymphoma in AD-HIES [36–39, 42], mainly non-Hodgkin lymphoma. Unlike other patients with marked IgE elevation, patients with AD-HIES do not appear to have an increased incidence of food allergy and are protected from anaphylaxis [43, 44]. While there is variability in the clinical phenotypes noted between AD-HIES patients, even those who carry the same mutation [36, 45], the overall phenotype does not vary remarkably.

Laboratory and Immunologic Features

The most prominent laboratory feature of AD-HIES is elevated serum IgE (>2000 IU/mL) in nearly all patients, although IgE levels can decrease over time [43]. Eosinophilia, both peripherally and in tissues, is also common. These laboratory features can be used with certain clinical features to assign a patient suspected of AD-HIES a score in the National Institutes of Health (NIH) scoring system [46], which can aid in diagnosis or raise sufficient suspicion to warrant *STAT3* sequencing. Patients with scores >40 are likely to have AD-HIES; in most large cohorts of AD-HIES patients 77–96% have NIH scores >40 [36–39].

AD-HIES patients typically have normal basic peripheral blood cell counts and basal IgG levels [28, 36]. However, further investigations into the specific cellular phenotypes of patients with AD-HIES have revealed a number of defects. The most notable of these is decreased, and often absent, numbers of Th17 cells [47–49], a finding which is consistent with the knowledge that Th17 cells are generated from naive CD4⁺ precursors in the presence of stimulation from multiple cytokines that signal through *STAT3* such as IL-6, IL-21 and IL-23 (reviewed in [50]). This deficiency is thought to drive several prominent aspects of immunodeficiency in AD-HIES patients, particularly the CMC [27]. However, AD-HIES patients chimeric for *STAT3* mutations [51] have Th17 cells but still had CMC. Therefore, *STAT3* may also serve an important host defense role in mucosal surfaces by transducing signals from IL-22 that promote the expression of anti-microbial peptides such as human beta defensin 2 and CC-chemokine ligand 20 [10, 43, 51].

The second major immunologic phenotype in AD-HIES is decreased T cell-dependent, antigen-specific antibody responses [28]. This finding appears due, at least in part, to a B cell-intrinsic defect that leads to decreased production of CD27⁺ memory B cells and plasma cells [28, 52, 53], although the memory B cells which are produced function normally [54]. Other reports have demonstrated decreased Tfh cells in AD-HIES [55], further impairing humoral immunity. Additional cell lineages reported to be abnormal in AD-HIES patients include central memory T cells [40, 56], mucosal-associated invariant T cells and NKT cells [57] and dendritic cells [58], but $\gamma\delta$ T cell numbers are normal [57].

A recent report described the generation of a mouse model of AD-HIES that recapitulated several aspects of human AD-HIES including elevated IgE, low Th17 cells [59], and resistance to anaphylaxis [44].

Genetics

Although there is autosomal dominant transmission of the *STAT3* mutations in AD-HIES, most patients have *de novo* mutations and only 6% of patients have a family history [38]. To date, 89 different mutations in *STAT3* have been described in AD-HIES (Figure 1), most of which are missense mutations [36, 39, 48, 52, 53, 60–63]. Unfortunately, no genotype-phenotype correlations have been established in AD-HIES [38, 39, 64], although some have suggested that the non-immune features of AD-HIES are enriched in patients with SH2 domain mutations [43].

Treatment

Most patients (90%) with AD-HIES are placed on prophylactic antibiotics in an attempt to avoid infection [36]. Approximately half of patients receive anti-fungal prophylaxis, this seems most appropriate for patients with chronic lung disease [36, 43]. Intravenous immunoglobulin treatment is used in about 50% of patients [36], and is typically reserved for those with low immunoglobulin levels and/or decreased specific immunity [43]. Proper skin care is also an important supportive measure [43].

Use of immunosuppressive medications in AD-HIES has been reported but is not typically employed [45]. Bone marrow transplantation has been performed with mixed results and has thus far not been aggressively pursued for AD-HIES [65–69].

SOMATIC *STAT3* GAIN-OF-FUNCTION

Five years following the reports of germline, loss-of-function mutations in *STAT3* as the cause of AD-HIES it was revealed that heterozygous, somatic mutations in *STAT3* leading to a gain-of-function were responsible for a major percentage (70%) of large granular lymphocytic (LGL) leukemias [5, 70]. LGL leukemias, derived from aberrant cytolytic lymphocytes, are indolent lymphoproliferative disorders of older patients (mean age 60) that account for 2–5% of chronic, lymphoproliferative disease [71]. Tumor-related *STAT3* mutations cluster in the SH2 domain (Figure 1) and lead to constitutive phosphorylation and upregulation of transcriptional activity [5, 71]. The increase in *STAT3* signaling resulting from the gain-of-function mutations is suspected to lead to cellular resistance to Fas-mediated apoptosis and lack of contraction following antigenic exposure [71].

While over-activation of STAT3, including constitutive phosphorylation, is a common feature of many malignancies, this is thought to be driven by abnormalities in upstream mediators such as receptor kinases [20]. Very few tumors, either hematologic or solid organ, have been reported to carry *STAT3* mutations outside of LGL leukemia (0.07%) [71]. A notable exception is inflammatory hepatocellular adenomas, which also carry activating mutations in other components of the IL-6 signaling pathway [72]. In addition, LGL leukemias frequently arise in the context of bone marrow failure in patients with aplastic anemia (AA) or myelodysplastic syndrome (MDS), and similar somatic *STAT3* gain-of-function mutations have also been noted in increased frequencies in both AA and MDS [73].

Of interest, patients with LGL leukemia, AA and MDS have an increased risk of concurrent autoimmune disorders, particularly cytopenias and rheumatoid arthritis (RA) [71]. Gain-of-function, somatic *STAT3* mutations were more likely to be present in LGL leukemia patients with concurrent RA (26% versus 6%) and are suspected to drive the autoimmune phenotype in addition to the lymphoproliferation [5].

GERMLINE *STAT3* GAIN-OF-FUNCTION

In the last year, three groups, including ours, have described a total of 19 patients with heterozygous, germline, *STAT3* gain-of-function (GOF) mutations initially discovered after examining variants in exome data generated from unique patients with early-onset and severe multi-organ autoimmunity [6–8]. *STAT3* GOF patients have features of other single-gene immune dysregulation disorders including autoimmune lymphoproliferative syndrome (ALPS), immunodeficiency polyendocrinopathy enteropathy x-linked (IPEX) and IPEX-like disorders, and *STAT5b*-deficiency [74, 75]. Given the diversity of the autoimmune phenotypes described in these initial patients, we suspect many additional patients with early-onset autoimmunity will be found to harbor *STAT3* GOF mutations; and we have already confirmed novel *STAT3* GOF mutations in several additional patients (unpublished observation).

STAT3 GOF patients developed symptoms at an average of 4.6 years of age (range 0–17 years). Hematologic autoimmunity is the most predominant feature, followed by lymphoproliferation (Table 2). Patients typically had more than one autoimmune disorder including enteritis, type I diabetes, thyroid disease, arthritis, lymphocytic interstitial pneumonia, hepatitis, and skin disease. Post-natal short stature is also a prominent feature of *STAT3* GOF.

The immune dysregulation in *STAT3* GOF leads to recurrent and/or severe infections in addition to autoimmunity, in particular respiratory infections. However, recognition of any specific pathogen susceptibility in *STAT3* GOF patients awaits additional reports. Despite the presence of somatic, *STAT3* gain-of-function mutations in malignancy as described above, only two patients have been reported with malignancy [7, 8]; one adult patient had Hodgkin lymphoma and one patient developed LGL leukemia at the age of 14. As these patients are mostly young children, it is possible that the incidence of LGL leukemia or other malignancy associated with *STAT3* GOF will increase with time. Additional isolated features are present in one or two patients including uveitis, thrombosis and mycobacterial

infection. Estimation of the true incidence of these findings in STAT3 GOF will require data from additional patients.

Lymphopenia and hypogammaglobulinemia are common in patients with STAT3 GOF, and eosinopenia was noted in three patients [8]. Some patients are seropositive for antibodies associated with autoimmune disease, such as anti-thyroid peroxidase antibodies, but overall autoantibody production does not appear to be a predominant feature of STAT3 GOF. Elevated double-negative T cells were found in some patients. A subset of three patients [8] had extensive immune phenotyping suggesting decreased, class-switched memory B cells, decreased numbers of plasmacytoid dendritic cells and decreased NK cell numbers with normal per cell function.

These initial studies in STAT3 GOF patients have been limited by the availability of patient samples and the concomitant use of immunosuppressives that alter lymphocyte function and development. However, STAT3 GOF patients appear to have decreased numbers of circulating FOXP3+ Treg cells with decreased intensity of CD25 and FOXP3, and impaired functional suppressive capacity [8]. This likely results, at least in part, from the role of STAT3 in the development and function of iTregs [76, 77]. We also observed decreased phosphorylation of STAT5 in cells from patients with STAT3 GOF, which could also contribute to Treg defects due to impaired IL-2 signaling [7, 78].

The numbers of peripheral blood Th17 cells in STAT3 GOF patients ranged from highly elevated (Patient 1 in [7]), to normal, to decreased [8]. In addition to being important for anti-fungal immunity, Th17 cells are also implicated in the development of autoimmunity [50]. Further, subsets of Th17 cells are beginning to be appreciated [50], along with the recognition of a certain degree of plasticity in the continuum between the existence of Tregs and Th17 cells [79, 80]. Therefore, while these preliminary analyses of STAT3 GOF patients did not demonstrate consistently elevated IL-17 production by peripheral blood T cells, it remains to be seen if future analyses can detect increased dysregulation of the Th17 axis.

The 19 reported STAT3 GOF patients collectively represent 13 different *STAT3* GOF mutations, most of which were novel (one was previously described in liver cancer and another in LGL leukemia). These mutants were, for the large part, *de novo*, but found to be inherited in two families [7]. Unlike the somatic *STAT3* gain-of-function mutations in LGL leukemias, germline *STAT3* GOF mutations were located throughout the molecule (Figure 1).

Unlike AD-HIES, patients with *STAT3* GOF mutations had markedly variable phenotypes, including two asymptomatic carriers of *STAT3* GOF mutations [7]. However, among these initial STAT3 GOF patients, the p.T716M mutation was present in 4 patients (including one father/son duo), and was associated with small bowel enteropathy in all patients with this mutation. It remains to be seen if this genotype-phenotype correlation holds up with future reports. Furthermore, *STAT3* polymorphisms have been reported in association with a number of autoimmune diseases such as psoriasis, ankylosing spondylitis, rheumatoid

arthritis and Crohn's disease [81–84]. It is intriguing to speculate that these variants may somehow confer hyperactivation and predisposition to autoimmunity.

The autoimmune manifestations of *STAT3* GOF patients were treated with a collection of immunosuppressants. After discovery of his *STAT3* GOF mutation, one patient was treated with targeted therapy using anti-IL-6 receptor antibody treatment (tocilizumab) [7], which has been approved for juvenile arthritis [85]. Despite failing multiple prior treatments, remarkable improvement in his arthritis and scleroderma-like skin changes were noted after initiation of tocilizumab, as well as the ability to wean his chronic prednisone dose. Two other *STAT3* GOF patients underwent bone marrow transplantation, one died of disseminated adenoviral infection and graft-versus-host-disease but the other patient had a successful transplant with resolution of her autoimmunity [7]. The orally available JAK inhibitor tofacitinib is approved for treatment of adults with RA [86, 87]. Use of tofacitinib has not yet been reported as treatment in *STAT3* GOF, but remains an enticing possibility.

THE MECHANISM OF *STAT3* IN HUMAN DISEASE

In addition to *STAT3*, human disease has been reported to result from mutations in 4 of the other 6 *STAT* molecules [88–95]. Defects in *STAT1* and *STAT5* also lead to immune dysregulation and immunodeficiency, and overlap in clinical phenotype with AD-HIES and *STAT3* GOF patients. Heterozygous *STAT1* LOF leads to susceptibility to mycobacterial disease [88], as has been reported in one *STAT3* GOF patient [8]. Complete *STAT1*-deficiency further predisposes to the development of lethal viral infections [89]. Like AD-HIES, *STAT1* GOF is a genetic cause of CMC with low Th17 cells [91, 92, 96]. However, a subset of *STAT1* GOF patients also has IPEX-like autoimmune disease with impaired Tregs which phenocopies *STAT3* GOF. Patients with *STAT5b* LOF have profoundly short stature and decreased Tregs, and are further similar to *STAT3* GOF patients due to recurrent infections and increased rates of autoimmunity, in particular lung disease [94].

Given their overlapping cytokine response profiles, similar DNA binding motifs and intersecting negative feedback loops it follows that an increase or decrease in the activation status of one *STAT* molecule can lead to alterations in others, ultimately resulting in similar functional outcomes [2, 18, 23]. Indeed, we observed impaired *STAT1* and *STAT5* phosphorylation in cells from *STAT3* GOF patients, which may explain some of the similarities among these syndromes [7]. By contrast, both *STAT1* and *STAT3* are hyperphosphorylated in the context of *STAT5b* LOF [94], while *STAT3* phosphorylation appears unaffected in *STAT1* GOF [92].

Only limited details regarding mechanisms behind the pathophysiology of *STAT* dysregulation in human disease are reported. Poor phosphorylation of *STAT3* has been shown in some AD-HIES SH2 domain mutants, along with decreased DNA binding of both DBD and SH2 domain mutants [97]. Somatic *STAT3* GOF mutations are associated with baseline hyperphosphorylation [5]. Germline *STAT3* GOF mutations do not appear to confer constitutive phosphorylation, although delayed dephosphorylation was demonstrated in cells from one patient [7]. In *STAT1* GOF both hyperphosphorylation and delayed dephosphorylation has been demonstrated [98]. The GOF in *STAT1* has been shown to be

dominant, as transcriptional activity was not decreased by co-transfection of wild-type STAT1 [98]. Conversely, co-transfection of wild-type and GOF STAT3 leads to a reduction in transcriptional activity of the mutant by approximately 50% (T.P.V. and M.A.C., unpublished observation), suggesting a dose-dependent effect.

Further elucidation of the mechanisms of these mutations will hopefully shed light on how STAT dysregulation syndromes can have overlapping phenotypes, as well as how the same or adjacent amino acids in STAT3 can be mutated into both a gain- and loss-of-function (Figure 1). Generation of additional STAT knock-in mouse models will be invaluable for these studies.

CONCLUSIONS

The recent reports of patients with germline *STAT3* GOF mutations have both combined and contrasted with our knowledge of germline *STAT3* loss-of-function mutations in AD-HIES to provide a more complete picture of the role of STAT3 in human disease. Further understanding of the mechanisms behind the gain- and loss-of-function in these mutations is needed, as it may be possible to apply this new understanding to the targeted treatment of conditions ranging from immune deficiency to malignancy to autoimmunity. As has now been identified for both STAT1 and STAT3, it is tantalizing to anticipate that the broad application of next generation sequencing in rare patients with immune dysregulation uncharacterizable by standard assessments may identify additional gain/loss-of-function dyads in human disease.

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References

1. Zhong Z, Wen Z, Darnell JE Jr. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. *Science*. 1994; 264(5155):95–8. [PubMed: 8140422]
2. Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. *Nat Rev Mol Cell Biol*. 2002; 3(9):651–62. [PubMed: 12209125]
3. Holland SM, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007; 357(16): 1608–19. [PubMed: 17881745]
4. Minegishi Y, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007; 448(7157):1058–62. [PubMed: 17676033]
5. Koskela HL, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. *N Engl J Med*. 2012; 366(20):1905–13. [PubMed: 22591296]
6. Flanagan SE, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. *Nat Genet*. 2014; 46(8):812–4. [PubMed: 25038750]
7. Milner JD, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. *Blood*. 2015; 125(4):591–9. [PubMed: 25359994]

8. Haapaniemi EM, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. *Blood*. 2015; 125(4):639–48. [PubMed: 25349174]
9. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. *N Engl J Med*. 2013; 368(2):161–70. [PubMed: 23301733]
10. Mogensen TH. STAT3 and the Hyper-IgE syndrome: Clinical presentation, genetic origin, pathogenesis, novel findings and remaining uncertainties. *JAKSTAT*. 2013; 2(2):e23435. [PubMed: 24058807]
11. UniProt C. UniProt: a hub for protein information. *Nucleic Acids Res*. 2015; 43:D204–12. Database issue. [PubMed: 25348405]
12. Ng IH, et al. Selective STAT3- α or - β expression reveals spliceform-specific phosphorylation kinetics, nuclear retention and distinct gene expression outcomes. *Biochem J*. 2012; 447(1):125–36. [PubMed: 22799634]
13. Shao H, Quintero AJ, Tweardy DJ. Identification and characterization of cis elements in the STAT3 gene regulating STAT3 α and STAT3 β messenger RNA splicing. *Blood*. 2001; 98(13):3853–6. [PubMed: 11739197]
14. Dewilde S, et al. Of alphas and betas: distinct and overlapping functions of STAT3 isoforms. *Front Biosci*. 2008; 13:6501–14. [PubMed: 18508676]
15. Maritano D, et al. The STAT3 isoforms α and β have unique and specific functions. *Nat Immunol*. 2004; 5(4):401–9. [PubMed: 15021879]
16. Chakraborty A, Tweardy DJ. Granulocyte colony-stimulating factor activates a 72-kDa isoform of STAT3 in human neutrophils. *J Leukoc Biol*. 1998; 64(5):675–80. [PubMed: 9823774]
17. Hevehan DL, Miller WM, Papoutsakis ET. Differential expression and phosphorylation of distinct STAT3 proteins during granulocytic differentiation. *Blood*. 2002; 99(5):1627–37. [PubMed: 11861277]
18. Villarino AV, et al. Mechanisms of Jak/STAT signaling in immunity and disease. *J Immunol*. 2015; 194(1):21–7. [PubMed: 25527793]
19. Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. *Immunity*. 2012; 36(4):515–28. [PubMed: 22520845]
20. Wake MS, Watson CJ. STAT3 the oncogene - still eluding therapy? *FEBS J*. 2015
21. Yang J, Stark GR. Roles of unphosphorylated STATs in signaling. *Cell Res*. 2008; 18(4):443–51. [PubMed: 18364677]
22. Decker T, Kovarik P. Serine phosphorylation of STATs. *Oncogene*. 2000; 19(21):2628–37. [PubMed: 10851062]
23. Carow B, Rottenberg ME. SOCS3, a Major Regulator of Infection and Inflammation. *Front Immunol*. 2014; 5:58. [PubMed: 24600449]
24. Wegrzyn J, et al. Function of mitochondrial Stat3 in cellular respiration. *Science*. 2009; 323(5915):793–7. [PubMed: 19131594]
25. Camporeale A, Poli V. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity? *Front Biosci (Landmark Ed)*. 2012; 17:2306–26. [PubMed: 22652781]
26. Takeda K, et al. Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality. *Proc Natl Acad Sci U S A*. 1997; 94(8):3801–4. [PubMed: 9108058]
27. Tangye SG, Cook MC, Fulcher DA. Insights into the role of STAT3 in human lymphocyte differentiation as revealed by the hyper-IgE syndrome. *J Immunol*. 2009; 182(1):21–8. [PubMed: 19109129]
28. Kane A, et al. STAT3 is a central regulator of lymphocyte differentiation and function. *Curr Opin Immunol*. 2014; 28:49–57. [PubMed: 24594518]
29. Fornek JL, et al. Critical role for Stat3 in T-dependent terminal differentiation of IgG B cells. *Blood*. 2006; 107(3):1085–91. [PubMed: 16223771]
30. Cui W, et al. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8⁺ T cells. *Immunity*. 2011; 35(5):792–805. [PubMed: 22118527]
31. Takeda K, et al. Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. *Immunity*. 1999; 10(1):39–49. [PubMed: 10023769]

32. Gotthardt D, et al. Loss of STAT3 in murine NK cells enhances NK cell-dependent tumor surveillance. *Blood*. 2014; 124(15):2370–9. [PubMed: 25185262]
33. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet*. 1966; 1(7445):1013–5. [PubMed: 4161105]
34. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics*. 1972; 49(1):59–70. [PubMed: 5059313]
35. Grimbacher B, et al. Hyper-IgE syndrome with recurrent infections--an autosomal dominant multisystem disorder. *N Engl J Med*. 1999; 340(9):692–702. [PubMed: 10053178]
36. Chandesris MO, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltimore)*. 2012; 91(4):e1–19. [PubMed: 22751495]
37. Jiao H, et al. Novel and recurrent STAT3 mutations in hyper-IgE syndrome patients from different ethnic groups. *Mol Immunol*. 2008; 46(1):202–6. [PubMed: 18706697]
38. Schimke LF, et al. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol*. 2010; 126(3):611–7. e1. [PubMed: 20816194]
39. Woellner C, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol*. 2010; 125(2):424–432. e8. [PubMed: 20159255]
40. Siegel AM, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. *Immunity*. 2011; 35(5):806–18. [PubMed: 22118528]
41. Chandesris MO, et al. Frequent and widespread vascular abnormalities in human signal transducer and activator of transcription 3 deficiency. *Circ Cardiovasc Genet*. 2012; 5(1):25–34. [PubMed: 22084479]
42. Wallet N, et al. Diffuse large B-cell lymphoma in hyperimmunoglobulinemia E syndrome. *Clin Lymphoma Myeloma*. 2007; 7(6):425–7. [PubMed: 17621409]
43. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. *Ann N Y Acad Sci*. 2012; 1250:25–32. [PubMed: 22268731]
44. Siegel AM, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. *J Allergy Clin Immunol*. 2013; 132(6):1388–96. [PubMed: 24184145]
45. Wolach O, et al. Variable clinical expressivity of STAT3 mutation in hyperimmunoglobulin E syndrome: genetic and clinical studies of six patients. *J Clin Immunol*. 2014; 34(2):163–70. [PubMed: 24452316]
46. Grimbacher B, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. *Am J Hum Genet*. 1999; 65(3):735–44. [PubMed: 10441580]
47. Milner JD, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008; 452(7188):773–6. [PubMed: 18337720]
48. Ma CS, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. *J Exp Med*. 2008; 205(7):1551–7. [PubMed: 18591410]
49. de Beaucoudrey L, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med*. 2008; 205(7):1543–50. [PubMed: 18591412]
50. Burkett PR, Meyer Zu Horste G, Kuchroo VK. Pouring fuel on the fire: Th17 cells, the environment, and autoimmunity. *J Clin Invest*. 2015; 125(6):2211–9. [PubMed: 25961452]
51. Hsu AP, et al. Intermediate phenotypes in patients with autosomal dominant hyper-IgE syndrome caused by somatic mosaicism. *J Allergy Clin Immunol*. 2013; 131(6):1586–93. [PubMed: 23623265]
52. Avery DT, et al. B cell-intrinsic signaling through IL-21 receptor and STAT3 is required for establishing long-lived antibody responses in humans. *J Exp Med*. 2010; 207(1):155–71. [PubMed: 20048285]
53. Meyer-Bahlburg A, et al. Heterozygous signal transducer and activator of transcription 3 mutations in hyper-IgE syndrome result in altered B-cell maturation. *J Allergy Clin Immunol*. 2012; 129(2):559–62. 562 e1–2. [PubMed: 22030463]

54. Deenick EK, et al. Naive and memory human B cells have distinct requirements for STAT3 activation to differentiate into antibody-secreting plasma cells. *J Exp Med.* 2013; 210(12):2739–53. [PubMed: 24218138]
55. Ma CS, et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. *Blood.* 2012; 119(17):3997–4008. [PubMed: 22403255]
56. Ives ML, et al. Signal transducer and activator of transcription 3 (STAT3) mutations underlying autosomal dominant hyper-IgE syndrome impair human CD8(+) T-cell memory formation and function. *J Allergy Clin Immunol.* 2013; 132(2):400–11. e9. [PubMed: 23830147]
57. Wilson RP, et al. STAT3 is a critical cell-intrinsic regulator of human unconventional T cell numbers and function. *J Exp Med.* 2015; 212(6):855–64. [PubMed: 25941256]
58. Saito M, et al. Defective IL-10 signaling in hyper-IgE syndrome results in impaired generation of tolerogenic dendritic cells and induced regulatory T cells. *J Exp Med.* 2011; 208(2):235–49. [PubMed: 21300911]
59. Steward-Tharp SM, et al. A mouse model of HIES reveals pro- and anti-inflammatory functions of STAT3. *Blood.* 2014; 123(19):2978–87. [PubMed: 24632714]
60. Zhang LY, et al. Clinical features, STAT3 gene mutations and Th17 cell analysis in nine children with hyper-IgE syndrome in mainland China. *Scand J Immunol.* 2013; 78(3):258–65. [PubMed: 23659370]
61. Sundin M, et al. Novel STAT3 mutation causing hyper-IgE syndrome: studies of the clinical course and immunopathology. *J Clin Immunol.* 2014; 34(4):469–77. [PubMed: 24627079]
62. Mogensen TH, Jakobsen MA, Larsen CS. Identification of a novel STAT3 mutation in a patient with hyper-IgE syndrome. *Scand J Infect Dis.* 2013; 45(3):235–8. [PubMed: 22992060]
63. Saikia B, et al. Hyper-IgE syndrome with a novel STAT3 mutation-a single center study from India. *Asian Pac J Allergy Immunol.* 2014; 32(4):321–7. [PubMed: 25543043]
64. Renner ED, et al. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced T(H)17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. *J Allergy Clin Immunol.* 2008; 122(1):181–7. [PubMed: 18602572]
65. Yong PF, et al. An update on the hyper-IgE syndromes. *Arthritis Res Ther.* 2012; 14(6):228. [PubMed: 23210525]
66. Goussetis E, et al. Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome. *J Allergy Clin Immunol.* 2010; 126(2):392–4. [PubMed: 20584545]
67. Nester TA, et al. Effects of allogeneic peripheral stem cell transplantation in a patient with job syndrome of hyperimmunoglobulinemia E and recurrent infections. *Am J Med.* 1998; 105(2):162–4. [PubMed: 9727824]
68. Gennery AR, et al. Bone marrow transplantation does not correct the hyper IgE syndrome. *Bone Marrow Transplant.* 2000; 25(12):1303–5. [PubMed: 10871737]
69. Patel NC, et al. Successful Haploidentical Donor Hematopoietic Stem Cell Transplant and Restoration of STAT3 Function in an Adolescent with Autosomal Dominant Hyper-IgE Syndrome. *J Clin Immunol.* 2015; 35(5):479–85. [PubMed: 25962528]
70. Jerez A, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. *Blood.* 2012; 120(15):3048–57. [PubMed: 22859607]
71. Rajala HL, et al. Uncovering the pathogenesis of large granular lymphocytic leukemia-novel STAT3 and STAT5b mutations. *Ann Med.* 2014; 46(3):114–22. [PubMed: 24512550]
72. Pilati C, et al. Somatic mutations activating STAT3 in human inflammatory hepatocellular adenomas. *J Exp Med.* 2011; 208(7):1359–66. [PubMed: 21690253]
73. Jerez A, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic syndrome patients. *Blood.* 2013; 122(14):2453–9. [PubMed: 23926297]
74. Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr.* 2013; 25(6):708–14. [PubMed: 24240290]

75. Oliveira JB, Fleisher T. Autoimmune lymphoproliferative syndrome. *Curr Opin Allergy Clin Immunol*. 2004; 4(6):497–503. [PubMed: 15640690]
76. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol*. 2010; 40(7):1830–5. [PubMed: 20583029]
77. Chaudhry A, et al. CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. *Science*. 2009; 326(5955):986–91. [PubMed: 19797626]
78. Cohen AC, et al. Cutting edge: Decreased accumulation and regulatory function of CD4+ CD25(high) T cells in human STAT5b deficiency. *J Immunol*. 2006; 177(5):2770–4. [PubMed: 16920911]
79. Komatsu N, et al. Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. *Nat Med*. 2014; 20(1):62–8. [PubMed: 24362934]
80. Gagliani N, et al. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature*. 2015
81. Tsoi LC, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet*. 2012; 44(12):1341–8. [PubMed: 23143594]
82. Danoy P, et al. Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. *PLoS Genet*. 2010; 6(12):e1001195. [PubMed: 21152001]
83. Seddighzadeh M, et al. Variants within STAT genes reveal association with anticitrullinated protein antibody-negative rheumatoid arthritis in 2 European populations. *J Rheumatol*. 2012; 39(8):1509–16. [PubMed: 22753649]
84. Barrett JC, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet*. 2008; 40(8):955–62. [PubMed: 18587394]
85. Frampton JE. Tocilizumab: a review of its use in the treatment of juvenile idiopathic arthritis. *Paediatr Drugs*. 2013; 15(6):515–31. [PubMed: 24155139]
86. van Vollenhoven RF, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012; 367(6):508–19. [PubMed: 22873531]
87. Lee EB, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014; 370(25):2377–86. [PubMed: 24941177]
88. Dupuis S, et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. *Science*. 2001; 293(5528):300–3. [PubMed: 11452125]
89. Dupuis S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet*. 2003; 33(3):388–91. [PubMed: 12590259]
90. Averbuch D, et al. The clinical spectrum of patients with deficiency of Signal Transducer and Activator of Transcription-1. *Pediatr Infect Dis J*. 2011; 30(4):352–5. [PubMed: 20962705]
91. van de Veerdonk FL, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011; 365(1):54–61. [PubMed: 21714643]
92. Liu L, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011; 208(8):1635–48. [PubMed: 21727188]
93. Hambleton S, et al. STAT2 deficiency and susceptibility to viral illness in humans. *Proc Natl Acad Sci U S A*. 2013; 110(8):3053–8. [PubMed: 23391734]
94. Kofoed EM, et al. Growth hormone insensitivity associated with a STAT5b mutation. *N Engl J Med*. 2003; 349(12):1139–47. [PubMed: 13679528]
95. Yildiz M, et al. Activating STAT6 mutations in follicular lymphoma. *Blood*. 2015; 125(4):668–79. [PubMed: 25428220]
96. McDonald DR. TH17 deficiency in human disease. *J Allergy Clin Immunol*. 2012; 129(6):1429–35. quiz 1436–7. [PubMed: 22554706]
97. He J, et al. STAT3 mutations correlated with hyper-IgE syndrome lead to blockage of IL-6/STAT3 signalling pathway. *J Biosci*. 2012; 37(2):243–57. [PubMed: 22581330]
98. Uzel G, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. *J Allergy Clin Immunol*. 2013; 131(6):1611–23. [PubMed: 23534974]

99. Kristensen T, et al. Clinical relevance of sensitive and quantitative STAT3 mutation analysis using next-generation sequencing in T-cell large granular lymphocytic leukemia. *J Mol Diagn*. 2014; 16(4):382–92. [PubMed: 24797340]
100. Ohgami RS, et al. STAT3 mutations are frequent in CD30+ T-cell lymphomas and T-cell large granular lymphocytic leukemia. *Leukemia*. 2013; 27(11):2244–7. [PubMed: 23563237]
101. Miyazaki K, et al. An adolescent with marked hyperimmuno-globulinemia E showing minimal change nephrotic syndrome and a STAT3 gene mutation. *Clin Nephrol*. 2011; 75(4):369–73. [PubMed: 21426892]
102. Giacomelli M, et al. SH2-domain mutations in STAT3 in hyper-IgE syndrome patients result in impairment of IL-10 function. *Eur J Immunol*. 2011; 41(10):3075–84. [PubMed: 21792878]
103. Al Khatib S, et al. Defects along the T(H)17 differentiation pathway underlie genetically distinct forms of the hyper IgE syndrome. *J Allergy Clin Immunol*. 2009; 124(2):342–8. 348 e1–5. [PubMed: 19577286]

Fig. 1. Schematic of the STAT3 protein showing the location of mutations reported to cause human disease

STAT3 is divided into 6 domains: the N-terminal domain (NT), coiled-coil domain (C-C), DNA binding domain (DBD), linker domain (L), Src-homology 2 (SH2) domain and transactivation domain (TA). Mutations shown above the figure represent missense mutations and the resulting amino acid changes, while mutations shown below the figure are deletions, duplications or intronic mutations represented in nucleotide nomenclature [6–8, 36, 39, 48, 52, 53, 60–63, 71, 72, 99–103]. Loss-of-function (LOF) mutations found in Hyper-IgE syndrome are indicated in green, those germline mutations reported in *STAT3* gain-of-function (GOF) are indicated in black, and the somatic, GOF mutations reported in malignancy, including LGL leukemia, are reported in blue. Malignancy-associated, somatic GOF mutations are clustered in the SH2 domain, whereas germline, GOF mutations are found throughout the protein. Most LOF mutations cluster in the DBD (42%) and SH2 domain (40%), where the highest number of unique LOF mutations are also found in the SH2 domain hot spot. The highest frequency LOF mutations representing the most patients are R382Q/W and V637M [39]. The intronic mutations surrounding exon 12 in the DBD (at c.1110 and c.1139) lead to a deletion of this short exon, D371_G380. The TA domain mutation c.2101+2332_o*STAT3*:c.2257+772del3933bp leads to the loss of exons 22 and 23, which are replaced with only a lysine residue

Table 1Frequency of Features in Germline STAT3 loss-of-function^a

Features	Percentage of Patients (n=214)
Skin	
Dermatitis	91–100%
Skin abscesses	85–100%
Neonatal Rash	45–74%
Infectious	
Pneumonia	87–100%
Pneumatoceles	45–77%
Upper respiratory infections	90%
Candidiasis	43–85%
Osteomyelitis	22%
Non-immune	
High palate	22–55%
Dysmorphic features	83–100%
Retained deciduous teeth	27–80%
Scoliosis	26–63%
Joint hyperextensibility	50–68%
Non-traumatic fractures	18–60%
Osteopenia	59% ^c
Vascular	
Coronary dilation	70%
Hypertension	54%
Focal hyperintensities on brain MRI ^b	70%
Laboratory	
Elevated IgE	96–100%
Hypereosinophilia	71–93%
Decreased Th17 cells	53–100%
B memory lymphopenia	95%
Lymphoma	7–9%

^aReferences [35–39].^bClinically silent.^cPercentage of patients with densitometry analysis.

Table 2Frequency of Features in Germline STAT3 gain-of-function^a

Features	Percentage of Patients (n=19)
Autoimmune	
Cytopenia(s)	74%
Lymphoproliferation	68%
Enteritis	47%
Skin disorder	42%
Type I diabetes	32%
Lung disorder	26%
Thyroid disorder	16%
Arthritis	16%
Organ systems with autoimmunity	
4	5%
3	32%
2	42%
1	21%
Non-autoimmune	
Short stature	63%
Malignancy	11%
Hypogammaglobulinemia	50%
Infectious	
Recurrent or severe infection	58%
Respiratory infection	26%
Herpes virus	16%
Bacterial sepsis	10%
Candidiasis	10%
Mycobacterial	5%
Soft tissue	5%

^aReferences [6,7,8].