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Germline STAT3 gain-of-function mutations in primary immunodeficiency: Impact on the cellular and clinical phenotype

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ABSTRACT

Signal transducer and activator of transcription 3 (STAT3) is a key transcription factor involved in regulation of immune cell activation and differentiation. Recent discoveries highlight the role of germline activating STAT3 mutations in inborn errors of immunity characterized by early-onset multi-organ autoimmunity and lymphoproliferation. Much progress has been made in defining the clinical spectrum of STAT3 GOF disease and unraveling the molecular and cellular mechanisms underlying this disease. In this review, we summarize our current understanding of the disease and discuss the clinical phenotype, diagnostic approach, cellular and molecular effects of STAT3 GOF mutations and therapeutic concepts for these patients.

Control of immune cell activation is critical to restore immune homeostasis after resolution of infections and to prevent immunopathology including autoimmune diseases. Uncontrolled expansion of immune cells is a hallmark feature of benign lymphoproliferation manifesting as lymphadenopathy and/or splenomegaly and of immune-cell derived malignancies. The combination of lymphoproliferation and autoimmunity or immunopathology, variably associated with increased infection susceptibility, is characteristic for a group of inborn errors of immunity that can be summarized as autoimmune-lymphoproliferative primary immunodeficiencies (AL-PID). In recent years, tremendous progress has been made in understanding the genetic and molecular mechanisms underlying this spectrum of diseases. Mutations in the FAS pathway were the first genetic variants identified to cause autoimmune-lymphoproliferative syndromes (ALPS) in the 1990s [1]. However, recent advances in genetics have allowed the discovery of defects in many other pathways that

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can lead to ALPS-like clinical presentations. They include disorders of the RAS-pathway, the PI3 Kinase pathway, JAK/STAT pathways, the NFkB pathway and the CTLA4 checkpoint pathway. Amongst these genes recently associated with an ALPS-like phenotype is STAT3 (Signal transducer and activator of transcription 3) [2–4].

Janus tyrosine kinases (JAKs) and STATs are crucial proteins in signal transduction initiated by a wide range of cytokines [5] and growth factors [6]. The important functions of the JAK-STAT signaling components in the control of the immune system homeostasis have been demonstrated by genetic knockout studies [7–9]. STAT3 is essential for vertebrate development [10] and plays a critical role in regulating key physiological functions in tissues, including the innate and adaptive immune responses [11]. It is therefore not surprising that activating or inactivating mutations in STAT3 result in human diseases such as immunodeficiency, autoimmunity and cancer. The discovery of inactivating (loss-of-function, LOF) germline heterozygous mutations in STAT3, which cause the Hyper-immunoglobulin E syndrome (HIES), first illustrated how STAT3 impacts human T and B lymphocyte function *in vivo* [12,13].

Phenotypic heterogeneity and incomplete clinical penetrance: the clinical picture of STAT3 GOF disease

Recently, several groups have identified germline gain-of-function (GOF) mutations in STAT3 as a cause for early onset multi-organ autoimmunity and lymphoproliferation [2–4]. While the first report identified germline STAT3 mutations in pediatric cohorts with early-onset diabetes, subsequent reports associated STAT3 GOF mutations predominantly with lymphoproliferation and autoimmunity [4]. Retrospective analysis of published case reports [14] and bigger cohort studies [15] now allow a more comprehensive definition of the clinical phenotype of STAT3 GOF disease [Fig. 1]. There is no obvious sex preference and the average age of onset of first symptoms is 3 years. However, it is important to note that not all mutation carriers become symptomatic and there are several reports of asymptomatic family members (15 asymptomatic of 83 reported cases, 18%) who carry the exact same mutation as the affected individual [4,14–16]. This suggests that the STAT3 mutation itself is not sufficient to trigger STAT3 GOF disease.

The most predominant symptoms are autoimmune cytopenia (63%), lymphoproliferation including splenomegaly and lymphadenopathy (63%), susceptibility to infections (66%), hypogammaglobulinemia, enteropathy and growth deficiency [Fig. 1]. Rarer manifestations include interstitial lung disease [17], endocrinopathies, arthritis [4] and erythropoiesis defects [18]. None of these features or combinations of features are sufficiently specific to delineate STAT3 GOF from other AL-PID diseases based on clinical findings. Notably, the occurrence of early onset (<2 y) diabetes mellitus type 1 [2,14,19,20] is rarely observed in other AL-PID diseases. However, this manifestation is not very sensitive since only 20% of the published STAT3 GOF patients have developed early onset diabetes. Another observation is that endocrine and gastrointestinal disease in STAT3 GOF patients usually manifest early in life and frequently appear before the onset of hematologic disease [14]. Hematological malignancy has only been reported in two cases [2,4] and seems to be rarer than in other AL-PID conditions [Fig. 1].

Currently ongoing comprehensive cohort studies will define the phenotype at higher resolution in the near future (Forbes et al., in preparation).

The STAT3 pathway and its molecular regulation

To understand the variety of immune alterations and the heterogeneity of the clinical presentation, a basic molecular understanding of the STAT3 pathway is required. The transcription factor STAT3 is activated by a wide range of ligands that bind cytokine receptors (e.g. interleukins, IL), receptor tyrosine kinases (e.g. epidermal growth factor, EGF; Platelet-derived growth factor, PDGF, fibroblast growth factor, FGF) or G-protein-coupled receptors. This broad role in a variety of receptor pathways explains the functional pleiotropy of STAT3: it is involved in inflammation, tissue regeneration, cell proliferation, cell survival, cellular differentiation, angiogenesis, chemotaxis and cell adhesion. Cytokines that activate STAT3 include those that bind to the Interleukin (IL)-6 family of cytokine receptors (e.g. IL-6, oncostatin M, IL-11), the homodimeric receptors (e.g. granulocyte colony-stimulating factor, G-CSF; Erythropoietin, EPO; growth hormone, GH), the IL-10 family receptors (e.g. IL-10, IL-19, IL-20, IL-22) [5] and the interferon receptors [31]. Upon cytokine binding, the receptor multimerizes and tyrosine kinases from the Janus kinase (JAK) family are brought into close proximity, allowing trans-phosphorylation [Fig. 2]. Subsequently, the activated JAKs phosphorylate the cytoplasmic tails of the receptor allowing STAT3 recruitment and further phosphorylation at the highly conserved tyrosine residue 705 (pY705), located in the trans-activation domain. STAT3 structurally comprises an N-terminal region followed by a coiled-coil domain (1–320), a DNA binding domain (DBD, 320–465), and a C-terminal region (465–770) which includes the Src Homology 2 (SH2) domain, and a C-terminal transactivation domain [Fig. 3]. After being phosphorylated by JAKs, active STAT3 forms homo- or heterodimers with other STATs and translocate to the nucleus to activate or repress transcription of target genes by mainly binding to the canonical '5-TTC(N3)GAA-3' consensus sequence or to the non-canonical sequences 'TTC(N3)AA' and 'TTC(N3)TAA' [32]. Additional alternative STAT3 binding sites have been reported [33].

Several post-translational modifications regulate STAT3 activity. Phosphorylation at serine 727 (pS727) by serine/threonine kinases like the mitogen-activated protein kinases (MAPK), mechanistic target of rapamycin (mTOR), and protein kinase C delta type (PKCδ) significantly enhances STAT3 transcriptional activity [34]. Additional modifications include lysine acetylation and methylation by protein acetyltransferases and methyltransferases [35], influencing STAT3 the dimerization, DNA binding and transcriptional activation.

The signaling strength, kinetics and specificity of the JAK-STAT pathway are modulated at several levels by three

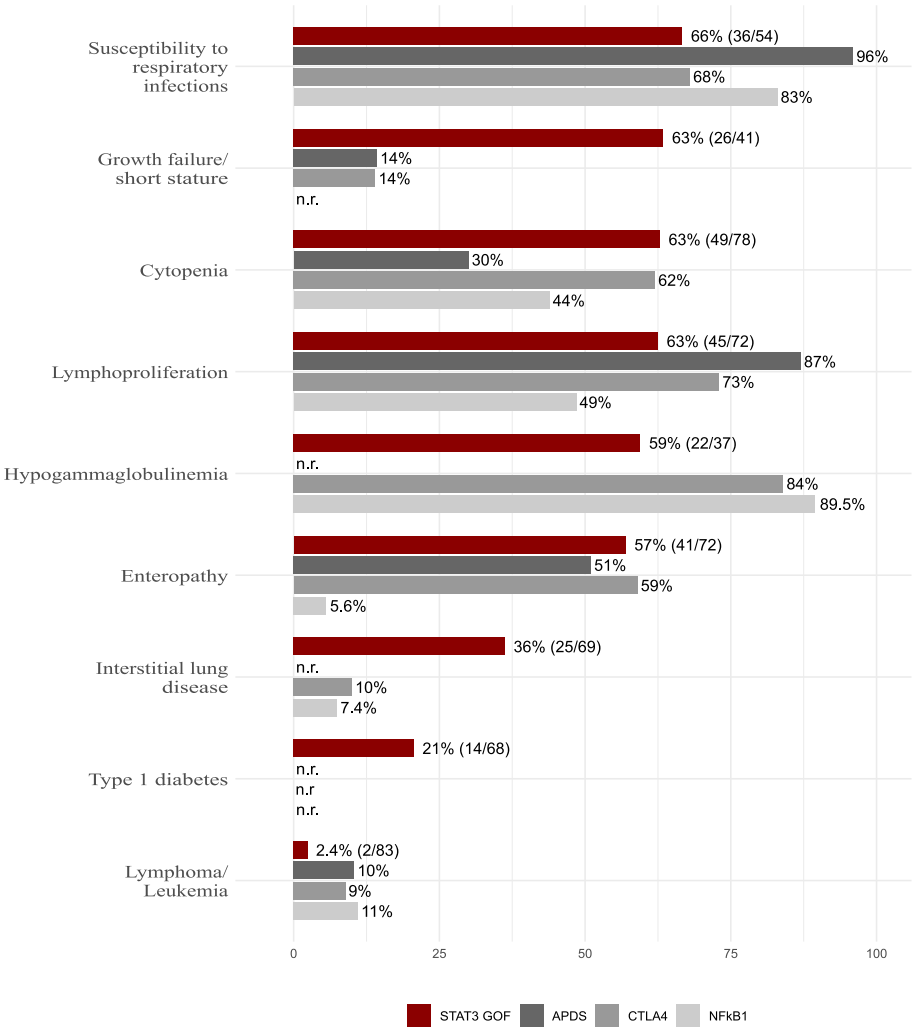

Fig. 1 Frequency of clinical symptoms observed in STAT3 GOF, APDS, CTLA4 and NFkB 1 associated diseases. Data from Ref. [14] were complemented with new patient reports from Refs. [15,16,21–27]. Patients appearing in more than one report were removed to the best of our ability resulting in a total of 83 STAT3 GOF patients. Reference values for APDS (n = 77), CTLA4 (n = 133) and NFkB1 (n = 157.) were taken from Refs. [28–30]. n.r.: not reported.

major negative feedback regulators. The primary negative regulator that switches off the signaling cascade at the level of the receptor is the STAT3 target gene SOCS3 (suppressor of cytokine signaling 3). SOCS3 engages with the IL6 family of cytokine receptors (bearing the subunit gp130) that contain binding sites for its SH2 domain, and inhibits the catalytic activity of JAKs preventing STAT3 phosphorylation [5]. Additionally, SOCS3 mediates the ubiquitination and subsequent proteasome degradation of other receptors, like the G-CSF and insulin receptor [36]. The second main regulatory mechanism consists of tyrosine phosphatases (e.g. PTPRC, PTPRT, and SHP1) that can dephosphorylate STAT3 dimers in the cytoplasm or in the nucleus. Finally, upon cytokine-mediated STAT3 activation, PIAS3 (protein inhibitor of activated STAT3) represses STAT3 in the nucleus preventing its binding to the DNA [37]. Additional regulation involves the direct targeting of STAT3 mRNA by microRNAs [38].

Apart from its pY705-dependent actions on gene transcription (canonical pathway), several additional functions have been attributed to STAT3. For example, unphosphorylated STAT3 operate as a transcription factor driving gene expression by mechanisms distinct from those used by pY705 STAT3 [39] and interacts with several components of the cytoskeleton to regulate cellular motility [40]. Serin-phosphorylated STAT3 localizes in the mitochondria (STAT3), where it modulates cell respiration and metabolism [41,42].

The molecular mechanisms of STAT3 GOF disease

Heterozygous mutations in STAT3 causing hyperactivation of the STAT3 pathway have first been associated with large granular lymphocytic leukemia (LGL), a clonal lymphoproliferative disorder mostly of $CD8^+$ T cells in which the mutation is present in a somatic form [43]. In contrast, STAT3 GOF associated autoimmune lymphoproliferative disease is

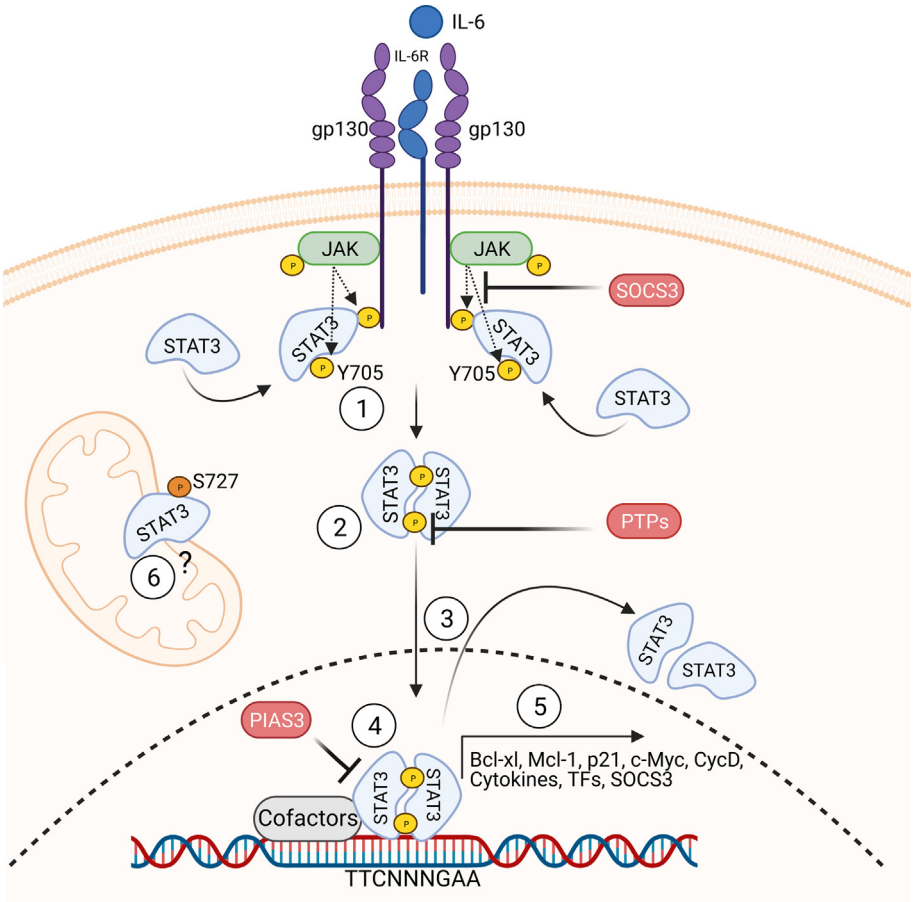

Fig. 2 Overview of the STAT3 signaling pathway. A cytokine (here IL-6) binds to its cognate receptor, which leads to phosphorylation of Janus Kinases (JAKs). Activated JAKs phosphorylate STAT3, which allows it to form dimers, shuttle to the nucleus and act as a transcription factor. The three main negative regulators of STAT3 activity are shown in red. SOCS3 inhibits the catalytic activity of JAKs preventing STAT3 phosphorylation, PTPs (phosphotyrosine phosphatases) dephosphorylate STAT3 dimers and PIAS3 prevents DNA binding of STAT3 dimers. In STAT3 GOF disease, the signaling cascade can be influenced at different levels leading to a variable combination of (1) increased phosphorylation or decreased dephosphorylation, (2) altered dimer formation (including heterodimers), (3) changes in nuclear translocation of the dimer, (4) altered DNA binding kinetics and motives and (5) changes in the target gene expression. The effect on non-canonical functions (6) and heterodimerization of different STAT molecules remains to be fully characterized.

caused by heterozygous germline mutations in STAT3. A simplified explanation for the dominant nature of these mutations (assuming that the mutation does not affect expression or dimerization) is that: 25% of the STAT3 homodimers will contain two GOF STAT3 molecules, 50% one wild type (WT) and one mutated molecule, while only 25% of dimers would function normally [44]. The gain-of-function effect of a given STAT3 variant is most commonly evaluated by expression of the mutant allele in a STAT3 deficient cell line followed by an *in vitro* luciferase assay. This test assesses transcriptional activity induced by binding of the STAT3 variant to a single defined STAT3-responsive element in the firefly reporter construct. If the mutation confers hyperactivity to STAT3 through increased binding to this element, this leads to an increased luciferase activity.

Since germline STAT3 GOF mutations associated with autoimmunity and lymphoproliferation have been described in all functional domains of the protein [Fig. 3] [15,45] it is expected that the different mutations exert their GOF effect at distinct steps of the signaling pathway, including phosphorylation, dimerization, interaction with other proteins, DNA binding or nuclear shuttling. Such molecular differences may contribute to the variability of the clinical or immunological phenotype [2–4,15]. Jägle et al. performed a comparative analysis of the molecular mechanisms underlying 17 distinct STAT3 mutations. The effect of the mutations on spontaneous and IL-6 induced canonical STAT3 signaling was assessed in reconstituted STAT3 deficient cell lines and primary patient cells. These results were correlated with the immunological and clinical manifestations [15] and suggested that most activating STAT3 mutations can be assigned to one of three groups defined by a distinct molecular response pattern. Group 1 mutations were characterized by an increased baseline activity in the luciferase assay and increased DNA

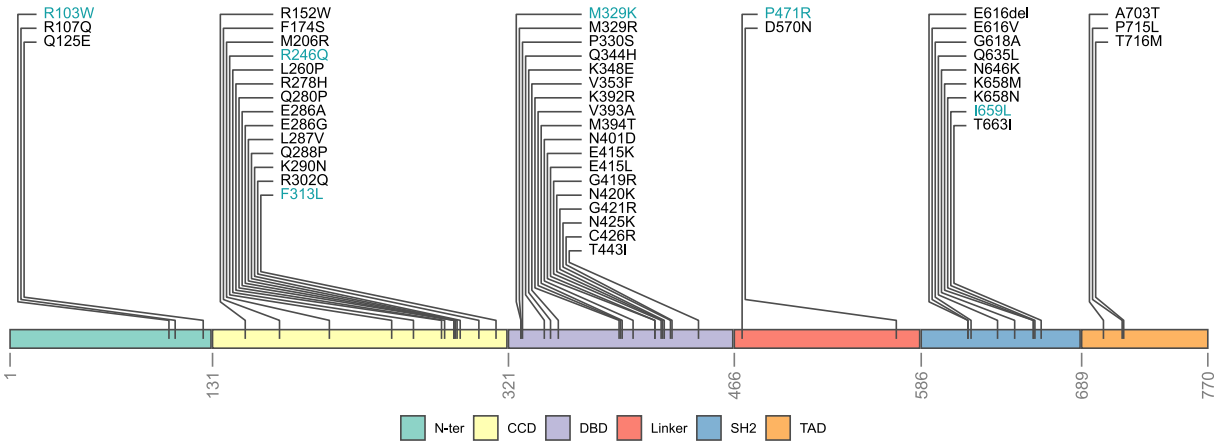

Fig. 3 Schematic of the STAT3 protein showing the location of all reported (02/2021) germline STAT3 GOF mutations within the STAT3 domains. All mutations were reported in at least one patient with clinical symptoms consistent with STAT3 GOF disease. For mutations depicted in black, GOF activity was confirmed by either *in vitro* testing using the luciferase assay or by increased pSTAT3 in *ex vivo* testing. For mutations depicted in green, no validation of GOF activity was reported. Detailed information can be found in Supplemental Table 1.

binding. Two group 1 mutations were shown to cause increased STAT3 phosphorylation in resting and stimulated cells, delayed dephosphorylation, and induced the highest expression of the STAT3 target genes, particularly SOCS3. This molecular pattern was associated with the highest penetrance of lymphoproliferation, autoimmune cytopenia and small stature among mutation carriers. Group 2 mutations only had a slightly increased basal transcriptional activity, that increased after stimulation to STAT3 WT. The other investigated molecular characteristics were variable and associated with moderately elevated STAT3 target gene expression, including SOCS3. Consistently, patients with group 2 mutations showed lower clinical penetrance. Group 3 mutants exhibited similar transcriptional reporter activity when compared to STAT3 WT. Nevertheless, they showed prolonged phosphorylation, increased DNA binding affinity and increased SOCS3 target gene expression, clearly confirming a GOF effect. Although these initial mechanistic observations require confirmation in more patients, they point towards a contribution of the specific mutation and the resulting molecular consequences to expressivity and penetrance of STAT3 GOF associated disease.

It is important to note that these studies did not cover other potential consequences of GOF variants such as the heterodimerization with other STAT molecules, like STAT1 and STAT5 [46–48]. STAT3 can also compete with STAT5 for DNA binding sites (e.g. antagonistic regulation of BCL6), with consequences for target gene expression [35]. Therefore, the relative abundance of STAT1, STAT3 and STAT5 may influence the amount/ratio of dimer formation and thus the biological outcome of the response to cytokines.

Additional complexity derives from the shared negative feedback mechanisms in STAT3 and STAT5 signaling via SOCS proteins. Milner et al. reported decreased STAT5 and STAT1 phosphorylation after treatment of patient-derived EBV cell lines with IL-2 and IFNγ, suggesting that STAT3 hyperactivity may lead to suppression of these STAT pathways. Moreover, patients with STAT5b LOF mutations show overlapping symptoms with STAT3 GOF patients (e.g. short stature, cytopenias, enteropathy) [49]. Reduced STAT5 phosphorylation and decreased STAT5b transcriptional activity was also observed by other groups in STAT3 GOF patient cells [18] and in HEK293-T cells transfected with STAT3 GOF variants [50].

Finally, GOF variants may also have an impact on the non-canonical functions of STAT3 and the cross-talk with other signaling pathways, for example the RTK/Ras/MAPK and PI3K/Akt pathways [51]. In cancers, mitochondrial STAT3 supports aberrant proliferation through its effects on the regulation of mitochondrial respiration and metabolism [52,53]. Activation of MAPK downstream RTK/Ras leads to the phosphorylation of STAT3 at S727 which enhances its transcriptional activity. Moreover, STAT3 activation indirectly promotes Ras signaling through the transcriptional activation of SOCS3, which diminishes the activity of the negative regulator RasGAP. Furthermore, S727-mitochondrial STAT3 was found to support Ras-dependent oncogenic transformation through the regulation of glycolysis and oxidative phosphorylation [42]. This indicates that activating mutations in STAT3 GOF patients may indirectly promote the activation of the Ras pathway. Additionally, the mutations may also impact the cellular distribution of unphosphorylated STAT3 and/or its interaction with the DNA, organelles and cytoskeletal proteins [54].

The immune cellular basis of STAT3 GOF disease

The functional consequences of the lack of STAT3 in the innate and adaptive immune system have been extensively reviewed [11,45,55]. Mice with conditional deletion of STAT3 in T and B cell lineages have revealed the essential role of STAT3 in the development of IL-17 producing $CD4^+$ T cells (Th17, [56]), the differentiation of T follicular cells (Tfh, [57]), the inhibition of the generation of $CD4^+$ T regulatory cells

(Tregs, [58]) and the differentiation of immunoglobulin G (IgG) secreting plasma cells [59]. Many of these features are illustrated by the clinical phenotypes and immune cell alterations observed in patients with HIES [12] (STAT3 LOF).

It has been more challenging to understand the cellular consequences of the activating germline STAT3 mutations in the biological function of primary human immune cells. Although some features such as reduced naïve $CD4^+$ T cells, elevated $CD57^+$ CD8 T cells, elevated double negative T cells, reduced NK cells, reduced memory B cells, hypogammaglobulinemia or neutropenia have been reported in some patients, other patients show normal values and there is no consistent pattern of these abnormalities [3,4,60]. STAT3/SOCS3 regulate critical steps during emergency granulopoiesis [11] and G-CSF signaling in neutrophils [61] - however neutropenia is not a consistent feature of the disease. Furthermore, reduced Treg function has been described in STAT3 GOF. Development of Tregs depends on IL-2 and STAT5 signaling [62]. It has been shown that SOCS3 negatively regulates responses to IL-2 [63]. Therefore, the upregulation of SOCS3 in STAT3 GOF variants may explain in part the inhibition of the function of these cells [63]. In addition, impaired STAT5 activation may also contribute to the decrease in T regulatory cell number. However, reduced Tregs numbers are only observed in some of these patients [4].

STAT3 controls key genes regulating proliferation (*Cyclin D1*, *c-Myc*, *PLK-1* and *Pim 1/2*) and apoptosis (*BCL-xL*, *BCL-2*, *MCL-1*, and *BIRC5*) [64,65]. It is therefore plausible that most patients with STAT3 GOF disease exhibit lymphoproliferation (hepatosplenomegaly and/or lymphadenopathy). Aberrant activation and overexpression of STAT3 is observed in many cancers [66,67], including leukemias and lymphomas [35] and has been shown to promote growth, survival, inflammation and stem cell phenotype maintenance in tumors. Hyperactive STAT3 in cancers is mainly associated with the aberrant activity of upstream signaling pathways, like EGFR, HER2 and JAK2 signaling. Somatic activating mutations in the STAT3 gene occur in hepatocellular adenomas, chronic lymphoproliferative disorders of NK cells (CLPD-NKs), diffuse large B-cell lymphomas [54] and in around 70% of T-cell LGL patients [68–70]. LGL is not only characterized by lymphoproliferation, but also by autoimmunity and autoimmune cytopenia, demonstrating that somatic mutations in T cells can recapitulate many features of the germline STAT3 GOF phenotype. Unlike most of the germline STAT3 GOF mutations, LGL associated STAT3 mutations predominantly occur in the SH2 region of STAT3 (e.g., Y640F, D661H, D661V, D661Y) and cause an increased phosphorylation and transcriptional activity [71]. Mechanistically, increased STAT3 activity was shown to increase resistance to FAS-mediated apoptosis [69,72]. Other authors reported that repression of STAT3 in LGL leukemic cells down-regulated the survival protein Mcl-1, resulting in an increased sensitivity to apoptosis [73]. Moreover, the balance of proapoptotic and antiapoptotic sphingolipid-mediated signaling was deregulated in LGLs [74].

Because of the pleiotropic functions of STAT3, the GOF variants also have an important impact on non-immune cell populations. Mauracher et al. described that the germline STAT3 GOF variant P715L led to a reduced response to stress erythropoiesis and concomitant anemia by interfering with the EPO-STAT5 signaling pathway [18]. Growth failure is another key clinical finding in STAT3 GOF patients [75] and insufficient responses to GH and primary insulin-like growth factor 1 (IGF-I) deficiency were previously reported [20,50]. The transcriptional activity of STAT5b was partially impaired in presence of STAT3 GOF variants, suggesting that the enhanced activity of STAT3 can lead to partial GH insensitivity [50]. Finally, interstitial lung disease (ILD) represents another example of an aspect of STAT3 GOF disease that may not only be immune cell related [17,26]. STAT3 is involved in the extracellular matrix remodeling mechanism during wound healing responses of fibroblasts [76,77] and has been implicated in mediating pulmonary fibrosis [78–82]. The crucial role of STAT3 signaling in fibrotic transformation together with the increased susceptibility to infections may explain the severe pulmonary manifestations observed in some STAT3 GOF patients (Gothe et al., submitted).

Diagnosing STAT3 GOF disease

Diagnosis of STAT3 GOF disease is challenging as neither specific clinical nor laboratory criteria exist. In the differential diagnosis to other autoimmune-lymphoproliferative diseases, early onset diabetes or growth failure should raise suspicion, but are by no means specific. Although most patients have some relevant immune cell alterations including a low number of switched memory B cells, reduced NK cells, reduced amounts of T regs or elevated double negative T cells (TCRab + CD4- CD8-) [3,15,45], none of these markers are sensitive or specific enough to be routinely used in diagnosis of STAT3 GOF. Low IgE levels have been suggested as a biomarker for STAT3 GOF disease, but testing IgE in larger cohorts revealed its insufficient sensitivity [83]. In our cohort of 52 AL-PID patients (28 with STAT3 GOF), sensitivity of IgE < 2 IU/ml was 39% whereas the specificity was 91% (unpublished data). Gene panel or exome analysis is therefore indicated for patients with a compatible clinical phenotype [84,85]. If previously unreported genetic STAT3 variants are found, their functional validation is important. *Ex vivo* PBMC assays investigating STAT3 phosphorylation or indirect assessments using STAT5 phosphorylation or SOCS3 expression have been successfully used to confirm GOF effects in individual patients [4,15,16,20,22], but at least in our hands they are not reliable enough to confirm or reject the diagnosis in all cases. The current gold standard for evaluating STAT3 variants is to express the mutation in a STAT3 deficient cell line followed by a luciferase reporter assay [2,4,15]. However, as discussed above, not all STAT3 GOF mutations are associated with increased luciferase activity. This may be explained by the fact that the test is based on a single STAT3 binding element and provides limited information on kinetics and dose response [15]. Therefore, in some cases more comprehensive studies including phosphorylation studies, DNA-binding and target gene expression assays are required to confirm the GOF effect of STAT3 mutations.

Treating STAT3 GOF disease

Autoimmune symptoms of STAT3 GOF patients have been treated with a broad spectrum of immunosuppressive medications. Retrospective analysis of published case reports and smaller case series indicated that systemic steroids only showed benefit in 3/17 patients [14]. Similarly poor treatment responses have been reported with mycophenolate mofetil (MMF) (2/5), Tacrolimus (1/4), Azathioprine (0/4) and Rituximab (1/3) [2,4,14,86–91]. However, there might be an ascertainment bias in retrospective analysis and ongoing larger cohort studies can hopefully provide more information on the use of non-targeted immunosuppressive agents in STAT3 GOF disease.

Other drugs allow direct targeting of the overactive IL6-JAK-STAT3 pathway. Tocilizumab is a monoclonal antibody against the IL6 receptor and Janus kinase inhibitors such as ruxolitinib act directly upstream of STAT3. Targeted immunosuppression with these agents has been successfully applied for the treatment of most of STAT3 GOF related symptoms including arthritis [4,86,91], interstitial lung disease [17,26,27,86] and enteropathy [22,27,92]. Several groups reported an additional benefit of combined treatment with tocilizumab and JAK-inhibitors in patients with severe ILD or severe enteropathy [27,86]. There is pharmacokinetic evidence to suggest that patients with STAT3 GOF might benefit from modified regimes with higher doses of ruxolitinib [27].

Hematopoietic stem cell transplantation (HSCT) has only been reported in a few patients with severe disease [4,20,21,50,86]. Out of 6 published patients 4 have died from complications after HSCT. In a recent survey by the EBMT 11/18 patients survived HSCT [93]. However, these numbers are still too small to judge the risks associated with HSCT and to appropriately weigh these risks against the spontaneous evolution of the disease including long-term immunosuppressive therapies. It is important to note that the growth deficit in some of these patients are not expected to be corrected by HSCT. Growth hormone (GH) treatment was reported to be (partially) successful in 7 patients [14] and only one reported patient did not respond to GH treatment [22]. Some patients have been reported with early onset and severe interstitial lung disease, which may have an epithelial component. It will therefore be important to closely monitor lung function both in transplanted as well as in non-transplanted patients in the future. Another important open question is whether full chimerism in all lineages will be needed for definite disease control.

Outlook

STAT3 GOF disease is a relatively common autosomal-dominant inborn error of immunity. Due to its phenotypic heterogeneity leading to initial presentation in very different medical subspecialties and its variable penetrance, it is likely underdiagnosed. The increasing number of patients will not only allow us to further define the clinical spectrum but also to gain further exciting insights into the role of STAT3 in orchestrating the human immune response. Currently it is unclear if a STAT3 GOF mutation itself is sufficient to drive disease or if external factors are needed. Drugs targeting the JAK-STAT signaling pathway offer excellent therapeutic possibilities in these patients. However, long-term effects and side effects must be closely monitored.

Many patients with autoimmune-lymphoproliferative phenotypes still remain without genetic diagnosis and it is likely that other genes involved in JAK-STAT signaling will be identified. For example, a recent report identified SOCS1 haploinsufficiency to be associated with early onset autoimmunity in a patient cohort that phenotypically shows large overlaps with STAT3 GOF patients [94]. It is also likely that related clinical phenotypes can be caused by somatic mutations in the JAK/STAT pathway leading to a proliferative advantage of disease-inducing immune cells, as has been described for a few patients with hypereosinophilic syndrome [95,96].

Whether the T cells of germline STAT3 GOF variants show a similar behavior as the somatic LGL variants regarding proliferation and impairment of apoptosis remains to be investigated. EBV-transformed cells from one STAT3 GOF patient and primary T cells from another GOF patient were more sensitive to death induced by the BCL-2 inhibitor ABT-737, indicating an impairment in apoptosis and a potential treatment approach [60]. Another question is which cells drive the lymphoproliferation in the liver, spleen and lymph nodes and whether a certain stimulus is required to trigger it.

Many aspects of STAT3 GOF disease are still not well understood on a molecular level. Genome-wide (single cell) transcriptomic studies could certainly shed light onto the mutation's effect on leukocytes including not only T-, B- and NK lymphocytes but also myeloid cells. Further unbiased DNA binding studies using e.g., ATAC Seq or Cut & Run Seq could help to elaborate altered binding motives and identify new transcriptional targets of mutated STAT3. This will hopefully lead to a more comprehensive understanding of the molecular and cellular consequences of germline STAT3 mutations that could have direct influence on patient treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2021.03.003.

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