

inside **blood** commentary

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Comment on Toubiana et al, page 3154

When the STATs are against you

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In this issue of *Blood*, Toubiana et al offer the fullest picture to date of the complex primary immunodeficiency caused by heterozygous gain-of-function (GOF) mutations of *STAT1*.¹

It has been 5 years since such mutations were first shown to cause an intriguing familial susceptibility to severe superficial fungal infection alongside autoimmune disease, often in the form of hypothyroidism.^{2,3} Since then, clinical immunologists have come to recognize *STAT1*-GOF as the major genetic etiology for chronic mucocutaneous candidiasis (CMC) disease (CMCD). The present international case series¹ highlights the broader immunodeficiency phenotype that accompanies CMC in such patients, contributing to severe morbidity and very significant early mortality. Inborn errors such as *STAT1*-GOF thus offer both a window into the human immune system and a grand challenge to advocates of precision medicine.

STAT1 encodes 1 of the STAT family of transcription factors that are activated by JAKs downstream of cytokine and interferon receptors.⁴ JAKs and STATs thus underpin contact-independent cell signaling throughout the immune system. The phosphorylated STATs translocate to the nucleus, form complexes with each other and with DNA to influence gene transcription, until they are deactivated by dephosphorylation. Different STATs talk to different receptors and genes but eavesdrop on each others' conversations. Too much *STAT1* seems to drown out the *STAT3* signal that is required to drive T cells toward the interleukin-17 (IL17)-producing, *Candida*-resisting T helper 17 (Th17) cell fate.³

Because IL17 is so important for antifungal immunity at epithelial surfaces, CMC results. A reciprocal defect in the form of *STAT3* loss-of-function (LOF) also predisposes to CMC but not to autoimmunity; this disorder is better known for the unpleasant staphylococcal infections of lung and skin that earn it the epithet "Job's syndrome."⁴

Toubiana et al have now coordinated an outstanding international effort to document the extended clinical phenotype of *STAT1*-GOF¹ (see figure). Biochemical confirmation that documented missense mutations were biochemically GOF was obtained in every case. By searching for and including family members who shared the *STAT1* genotype of individuals presenting with CMCD, they show that this disorder is fully penetrant with a median age of onset of only 12 months. The vast majority (98%) of individuals suffered CMC that frequently (75%) required long-term antifungal therapy and often (~30%) went on to develop resistance, leading to years of discomfort and complications including difficulty swallowing and cancerous change, especially of the esophagus.

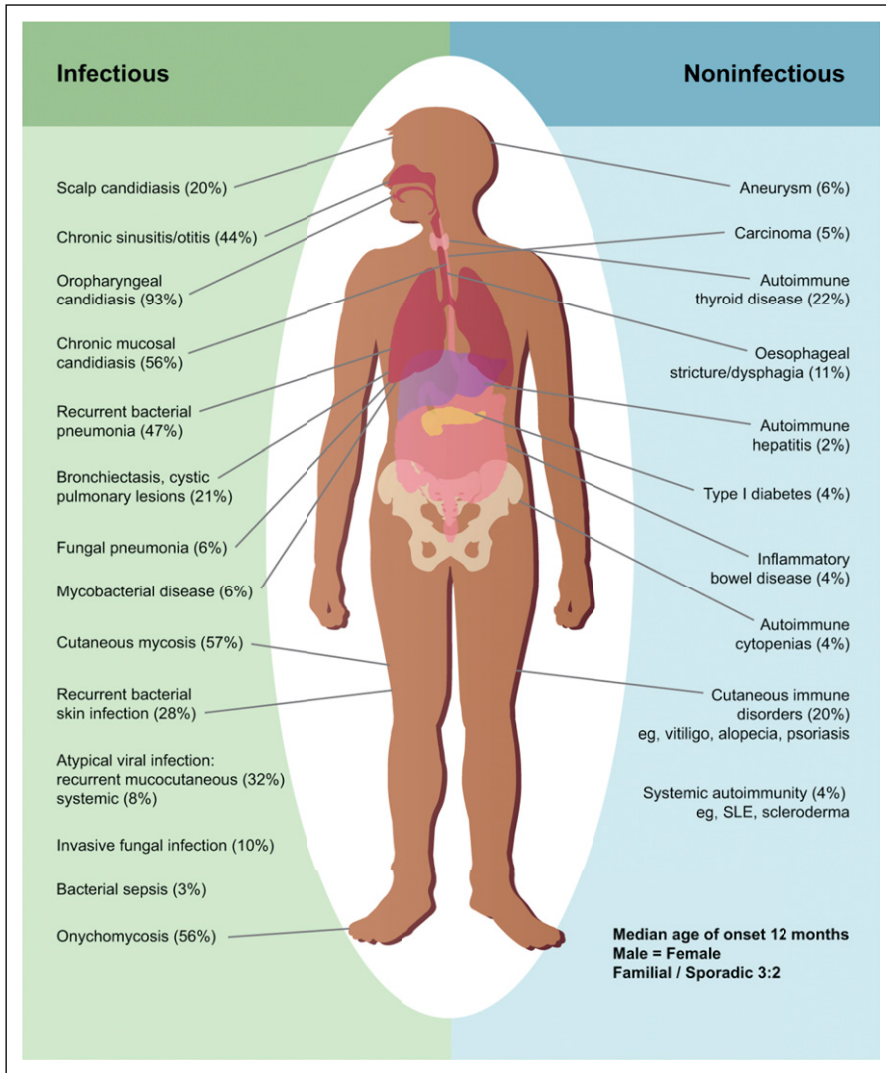
That *STAT1*-GOF causes CMC is not new, but among the most striking results of this study are the very high rates of bacterial and viral infection afflicting these patients, as well as invasive fungal infection and nontuberculous mycobacterial disease. Sinopulmonary infections were extremely common and led to

structural lung damage in around one-fifth of patients. Mucocutaneous involvement was not confined to mycosis but included bacterial skin infections in more than one-fourth of patients and atypical viral disease in one-third (especially zoster, herpes simplex; also warts and molluscum).

Among noninfective complications, aneurysm was documented in 6% of patients, mostly cerebral; as in patients with *STAT3*-LOF, this constitutes a significant mortality risk and Toubiana et al recommend systematic radiological screening. Autoimmune phenomena covered a wide range, from type I diabetes to scleroderma, and many more patients showed autoantibody production. Immunological hallmarks suggested by earlier studies were not universal, although many of those tested had low Th17 cell numbers and around one-half had reduced memory B cells. Patients with low B-cell or CD4 cell numbers were at greater risk of invasive infection.

Given the extent and severity of complications, it is not surprising that survival was significantly impaired. Deaths were predominantly due to invasive infection, cancer, and cerebral hemorrhage secondary to aneurysm. These occurred across the life course, at a median age of 30 years. Although not measured in this study, we can expect that quality of life was significantly impaired in the majority of patients who remained symptomatic from their CMC and/or bronchiectasis. This represents a substantial burden of morbidity and mortality for a childhood onset primary immunodeficiency.

These findings emphasize that *STAT1*-GOF is not a pathogen-specific disorder but instead should be considered a combined immunodeficiency. In keeping with this concept, there is already clear evidence that *STAT1*-GOF impacts not only Th17 generation³ but also T follicular helper cell phenotype and effectiveness and B-cell memory.^{5,6} Because cytokines and interferons provide critical contextual cues that



Infective and noninfective complications of GOF mutations in STAT1. Data derived from Toubiana et al. SLE, systemic lupus erythematosus. Professional illustration by Alison Schroeer, Schroeer Scientific Illustration.

influence lymphocyte polarization and behavior, this is perhaps not surprising.

Undoubtedly, we have more to learn about the subtleties of JAK-STAT biology within the immune system, but can we use existing knowledge for patient benefit? Targeted therapy is the holy grail that would allow us to treat inborn errors pharmacologically with minimal side effects. Arising from the understanding that STAT1 signaling remains JAK-dependent, 2 groups have recently

reported use of the JAK inhibitor ruxolitinib in STAT1-GOF, with positive benefit in both (although much more marked in 1 patient⁷ than the other⁸). Administration of granulocyte colony-stimulating factor, a plausible means to boost STAT3 signaling that appeared miraculously effective in 1 patient⁹ produced no benefit in another.¹⁰ We are therefore only at the beginning of the long road to precision medicine for STAT1-GOF, and the generation of a faithful knock-in mouse model

may be a crucial stepping stone to future clinical trials. Meanwhile, the curative potential of hematopoietic stem cell transplant for STAT1-GOF is beginning to be explored and an international survey of experience to date is currently being compiled.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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