Invited Review

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Identification of a Novel Primary Atopic Disorder due to STAT6 Gain-of-Function Mutations

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Abstract

Human inborn errors of immunity (IEI) are a group of distinct genetic disorders affecting children and adults, leading to recurrent infections, immune dysregulations, and malignancies. Over the course of the past decades, this area of research has witnessed significant progress in describing numerous monogenic disorders. A subset of IEI, which manifests as severe allergic disorders, recently termed "primary atopic disorders", now encompasses over 30 monogenic defects. Notably, the Janus kinase (JAK)-signal transducer and activator of transcription 6 (STAT6) signaling pathway plays a pivotal role in mediating allergic responses and developing primary atopic disorders. Herein, we detail a newly described IEI disorder due to gain-of-function mutations in STAT6 associated with severe allergic dysregulation. We outline its underlying mechanisms and present therapeutic approaches to its management.

Keywords: Inborn errors of immunity, primary atopic disorder, genetic, HyperIgE, JAK-STAT6 pathway, gain-of-function, targeted therapy

Introduction

The most recent classification of human inborn errors of immunity (IEI) by the International Union of Immunological Sciences offers an expansive list of single gene defects responsible for unique IEI, now reaching 485 genes (1). Relevant to this review are several monogenic IEIs that give rise to disorders characterized by severe allergic dysregulation as a key disease manifestation. These disorders, termed *primary atopic disorders*, have expanded from the original description of the paradigmatic hyper IgE syndrome (HIES) to now include more than 30 separate disorders (2). Historically, HIES was first defined in two girls with recurrent respiratory infections, severe dermatitis complicated with staphylococcal skin infections without inflammation signs, called a cold abscess, were described in 1966 (3). More than four decades late, dominant-negative mutations in signal transducer and activator of transcription (*STAT3*) were identified to cause the autosomal dominant form of this disease (AD-HIES) (4). These mutations resulted in defective responses to a number of cytokines, including interleukin (IL)-6 and IL-10, that normally mobilize STAT3 to convey their signals to the nucleus. These pioneering studies helped to elucidate pathogenic mechanisms operative in AD-HIES, a critical one of which involved severely reduced IL-17 production due to insufficient STAT3 signaling important for the development of Th17 cells (5,6). In turn, diminished production of IL-17, a cytokine necessary for effective mucosal immunity and antimicrobial peptide responses, promoted recurrent candidal and *Staphylococcal* infections observed in the mutation-bearing patients (7). Following this seminal discovery, many other genes were identified

to be causative for other subtypes of HIES, including mutations in *DOCK8, PGM3*, *ZNF341*, *IL6ST*, *IL6R*, *ERBIN*, *TGFBR1*, *TGFBR2,* and *CARD11* genes (1).

With the increased international collaborations between different centers involved in IEI research including those of the current authors, new fertile investigational studies were carried out (8-16). A case in point is our recent collaboration on investigating a novel atopic disorder that culminated by the discovery of a new germline STAT6 gain-of-function (GOF) disease (OMIM #620532, Hyper-IgE syndrome 6, autosomal dominant, with recurrent infections) (17), now expanded to at least 21 patients identified by several different groups (18-20). The STAT family consists of seven protein partners encoded by different genes, annotated as *STAT1*, *STAT2*, *STAT3*, *STAT4*, *STAT5A*, *STAT5B*, and *STAT6* (21). As alluded to above for STAT3, these molecules serve as critical immunological rheostat within the intricate regulatory network of the immune system. These molecules play a pivotal role in modulating innate and adaptive immune responses, finely tuning the delicate balance between immune activation and regulation. STAT6 is the essential transcription factor that perpetuates the biological effects of IL-4 and IL-13. The binding of IL-4 and IL-13 to IL-4R complexes begins the phosphorylation of conserved tyrosine residues in the cytoplasmic domain of the common IL-4 receptor alpha (IL-4Rα) subunit by the receptor-associated Janus kinases (JAK). STAT6 is subsequently recruited by binding its tandem Src homology 2 (SH2) domains to the IL-4Rα phosphotyrosine docking sites. Then, STAT6 is phosphorylated by the JAK kinases, leading to its dimerization and translocation into the nucleus to provide immune responses by activating the expression of target genes (22,23). The IL-4R-STAT6 axis is critical in type 2 immunity, directing protective responses to parasites and toxins, promoting B cell development, activation and class switching to IgE and IgG1, and directing overall tissue repair (24). Therefore, its dysregulation plays a pathogenic role in different allergic diseases (25). In our own studies, we showed for the first time the impact of alterations in immune cell responses, including T and B-cells, downstream of dysregulated STAT6 signaling, which were reversed by JAK inhibitor. Therapy with the same inhibitor also achieved disease control in the index case.

Case study: The Identification of STAT6^{E372K} Gain of Function Mutation

An illustrative example of the phenotype of STAT6 GOF disease was provided by a case study we recently reported (17-20). The index case presented in the newborn period with severe atopic eczema, intractable itching, severe growth retardation, generalized lymphadenopathy, and pneumonia (Figure 1). The eczema was associated with IgE responses to several aero and food allergens, including elevated specific serum IgE to mite, grass, wheat, soy, cow milk, egg, tomato, kiwi, almond, and nuts. He displayed dysphagia with vomiting following intake of wheat products, egg white, and tomato. In his physical examination later in childhood revealed severe chronic lichenified eczematous skin lesions, coarse facial appearance and lymphadenopathy, as well as other manifestations, including hyperextensibility and enamel hypoplasia. His gastrointestinal endoscopy revealed findings of eosinophilic esophagitis and colitis. Given the severity and chronicity of his allergic inflammation, whole exome sequencing analysis revealed a novel heterozygous variant in the *STAT6* gene at the DNA binding domain (c.1114G>A, p.E372K). The mutation showed increased STAT6 activation in the primary patient's lymphocytes and also when expressed in cell lines, as evidenced by elevated phosphor(p)-STAT6 at baseline and following IL-4 treatment in association with increased nuclear translocation and transcription of the mutant STAT6 after IL-4 stimulation compared to wild-type STAT6 (Figure 1). Furthermore, the dysregulated STAT6 activity was associated with Th2 cell-like skewing of T effector cells, T follicular helper cells (Tfh), and Treg cells, a phenotype indicative of dysregulated allergic inflammation. The clinical and immunological findings of STAT6 GOF are summarized in Figure 2. These results emphasize the early onset and severity of allergic inflammation affecting multiple tissues in STAT6 GOF disease.

Expanding the Clinical Spectrum of STAT6 GOF Disease

Together with our case, a total of 21 patients with *STAT6* GOF mutations have been reported so far in four separate reports (Table 1) (17-20). Akin to other dominant inheritance models, this disease presents mostly *de novo* with complete penetrance. All reported patients showed similar phenotypes to our case, which were characterized by early onset in infancy of severe atopic dermatitis and multiple food allergies (IgE and non-IgE mediated). Some patients also exhibited gastrointestinal (GI) involvement due to massive eosinophilic infiltration, asthma, anaphylaxis, drug allergies, recurrent skin infections with bacterial (*Staphylococcus aureus*), fungal (*Candida albicans*) and viral strains (*Molluscum contagiosum*), and respiratory tract infection (*Staphylococcus aureus*). Less commonly, two patients were reported with protein-losing enteropathy and intestinal polypoid nodules in the intestinal tract (18,19).

Systemic HIES findings of skeletal hypermobility, coarse face, pathogenic fractures, and vascular anomalies can also be observed in some patients, all of which were also prominent in our reported case (17,20). The mechanistic basis for the phenotypic overlap of

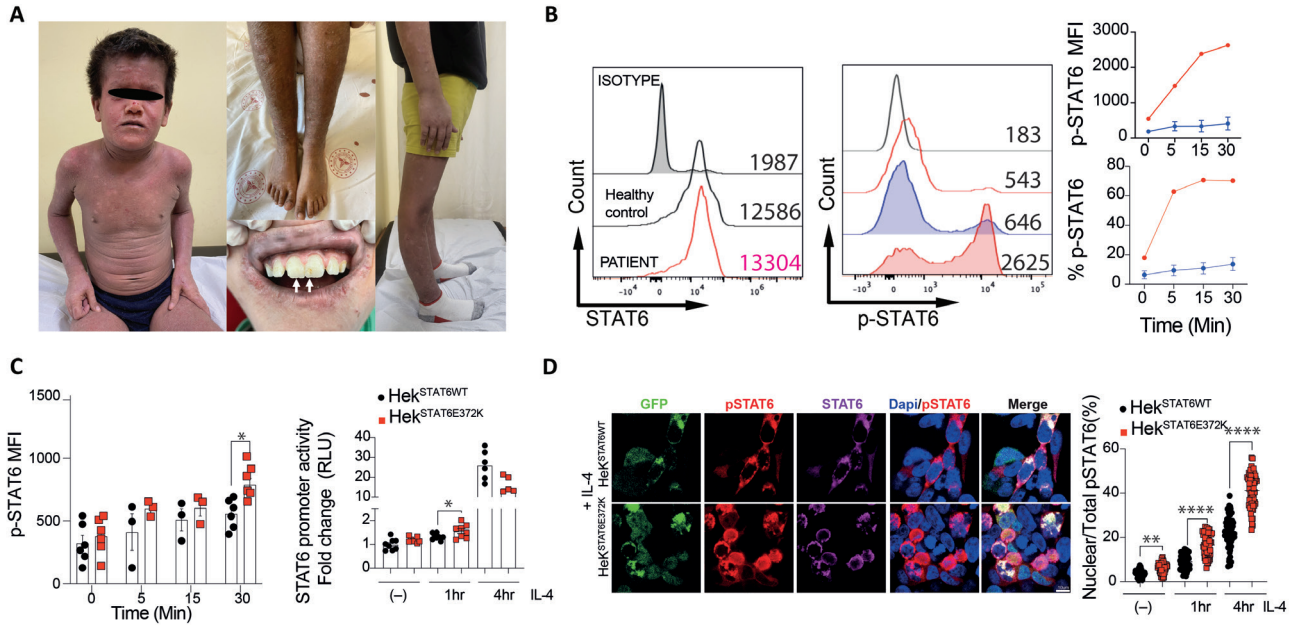

Figure 1. The clinical and immunological features in STAT6^{E372K} GOF mutation. A) Severe eczema with enamel hypoplasia and extremity hypermobility. B) Flow cytometric analysis and mean fluorescence intensity (MFI) of STAT6 in CD4^{+} T cells of healthy controls and the patient with STAT6^{E372K} mutation. C) MFI of pSTAT6 in HEK293 cells transfected with either STAT6^{WT} or STAT6^{E372K} proteins after IL-4 (20 ng/mL) stimulation for 5-30 minutes. D) STAT6 response element-driven luciferase reporter activation by STAT6^{WT} or STAT6^{E372K} transfected into HEK293 cells at baseline and following IL-4 treatment for 1 and 4 hours.
STAT6: Signal transducer and activator of transcription 6, IL: Interleukin, adapted after reference 17

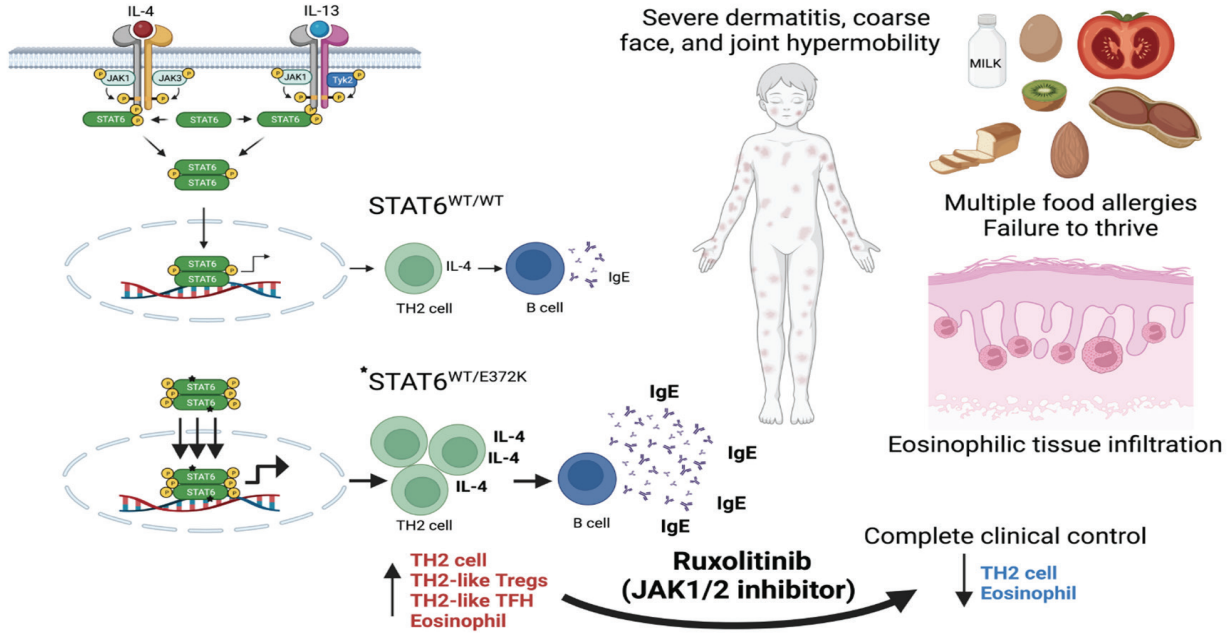

Figure 2. Immune mechanisms and targeted therapy in STAT6 GOF disease. Created by BioRender.
STAT6: Signal transducer and activator of transcription 6, GOF: Gain-of-function, adapted after reference 17

STAT6 GOF disease with the AD-HIES due to STAT3 mutations has hitherto not been investigated. However, the augmented function of STAT6 in response to IL-4 and IL-13 signals can potentially interfere with transcriptional activities of STAT3, especially as relates to downstream leukemia inhibitory factor receptor (LIFR) and IL-11R responses (26). It is well known that LIFR-deficient patients have osteoporosis, spontaneous fractures, joint

Table 1. The clinical and immunological presentations in 21 reported STAT6 GOF patients

Clinical and immunological features	n (%)
Infant onset	20 (95)
Severe extensive treatment resistant dermatitis	19 (90)
Multiple food allergies	17 (80)
Asthma	13 (62)
Anaphylaxis	11 (52)
Drug allergies	7 (33)
Recurrent respiratory infections (*S. aureus*)	6 (29)
Recurrent skin infections (*S. aureus, C.albicans, molluscum contagiosum*)	8 (38)
Recurrent viral infections (unspecified)	2 (9)
Eosinophilic gastrointestinal disease (non-IgE mediated)	15 (71)
Protein-losing enteropathy and polypoid nodules	2 (9)
Other GI problems (diarrhea)	3 (14)
Skeletal hypermobility	4 (19)
Osteoporosis, pathologic fracture	3 (14)
Coarse face	2 (9)
Enamel hypoplasia	2 (9)
Vascular anomalies	2 (9)
B-cell lymphoma	1 (4)
Marginal high IgE levels	21 (100)
Blood eosinophilia	21 (100)
Growth failure	9 (43)

STAT6: Signal transducer and activator of transcription 6, GOF: Gain-of-function, GI: Gastrointestinal

hyperextensibility, and scoliosis (27). On the other hand, IL-11R deficiency is associated with cranial dysostosis and dental anomalies (28). Impairment of LIFR and IL-11R responses by STAT6 GOF mutants may thus explain some non-immunological manifestations in STAT6 GOF disorder. Conversely, some classical AD-HIES infections associated with Th17 cell deficits such as chronic mucocutaneous candidiasis or other fungal agents were not observed in STAT6-GOF patients. While the Th17 cell compartment was decreased to some extent in our patient (17), the IL-17 pathway may not be as affected in STAT6 GOF disease as it is in AD-HIES, thus offering protection against fungal disease (18).

Interestingly, enhanced STAT6 activity due to somatic *STAT6* mutations have previously been identified in malignancies, and in particular in Hodgkin and non-Hodgkin lymphomas (29). Accordingly, the oldest patient with germline *STAT6* GOF disease reported to date by Sharma et al. (20) developed follicular and diffuse large B-cell lymphoma, indicative of the vulnerability for malignant transformation in this disease. In total, two of the 21 reported patients with STAT6 GOF disease have died (10%), one from anaphylaxis and the other from a cerebral aneurysm (20,30).

Understanding the Molecular Mechanisms in STAT6 GOF Disease

STAT6 has a critical role in the development of Th2 responses, as established in several mouse models. STAT6-deficient mice were shown to be highly resistant to allergic airway inflammation (31,32). In contrast, by performing an extensive mutational analysis, Mikita et al. (33) identified a GOF STAT6 mutant that contains alanine substitutions in the positions of V547A/T548A in the SH2 domain of STAT6 (STAT6VT), promoting allergic inflammation. The STAT6VT was activated independently of IL-4 stimulation and showed to be phosphorylated, dimerized, and activated the transcription of an IL-4 responsive promoter (34). The other indirect activation of STAT6 was described in a mouse model having an inactivating mutation (IL-4RaY709→F) in the immunotyrosine inhibitory motif (ITIM) in the cytoplasmic domain of the IL-4Rα chain (35). This missense mutation enhances STAT6 activation by inhibiting the recruitment of phosphotyrosine phosphatase Shp1 to the mutant receptor. The mutation promoted Th2 polarization, characterized by augmented basal and antigen-induced IgE responses and enriched allergen-induced eosinophilic airway inflammation and hyperreactivity. Overall, these mouse models clearly established the capacity of enhanced STAT6 function to foster allergic disorders.

Molecularly, the reported human STAT6 GOF mutants exhibited variable attributes: Some showed enhanced pSTAT6 levels at baseline and after stimulation, accompanied by increased nuclear translocation of pSTAT6 (17). Others showed normal pSTAT6 induction and dephosphorylation but enhanced nuclear STAT6 accumulation in the nucleus (18). Yet others showed enhanced pSTAT6 levels only after stimulation (19), or normal phosphorylation but decreased dephosphorylation patterns (20). On the other hand, augmented levels of STAT6 protein were observed in two subjects including our own, though the increase in our patient was mild (17,30). Interestingly, enhanced STAT6 nuclear localization in the absence of cytokine stimulation was also reported in some patients (18,19). Notwithstanding these discrepancies, common features among the majority of the STAT6 GOF mutants include augmented STAT6 nuclear translocation and a propensity for positively charged amino acid substitutions in the DNA binding domain that may accentuate binding to negatively charged target DNA. These GOF attributes drive skewing to Th2 responses in effector $CD4^+$ T, Treg, and T_{FH} cells with diminished Th1 and Th17 responses (18-20). There was also an enhanced B-cell switching to IgE with increased CD23 and IL4Rα expressions in tested B-cells of patients (17,20). All these dysregulated responses explain the drastically increased IgE and eosinophilia, which are observed in all reported 21 patients. Of note, unlike some

Table 2. Described disorders associated with STAT mutations

STAT subtypes	Inheritance and function	Clinical and immunological phenotype
STAT1	AR, LOF	Partial form: Mild mycobacterial and viral infections Complete form: Fatal mycobacterial and viral infections Impaired STAT1-dependent IFN-α/β and λ responses
STAT1	AD, LOF	Mycobacterial infections and *Salmonella*, Impaired IFN-γ signaling
STAT1	AD, GOF	Chronic mucocutaneous candidiasis Increased susceptibility to bacterial and viral (herpesviruses), invasive fungal infections Multiple autoimmunity like IPEX phenotype Squamous cell carcinoma Cerebral aneurysm Decreased Th17 and increased Th1 responses
STAT2	AR, LOF	Severe viral infections (disseminated vaccine strain measles) Impaired STAT1-dependent IFN-α/β and λ responses
STAT2	AR, GOF (R148 variant)	Life-threatening autoinflammation with type I interferonopathy Phenocopy of USP18 deficiency Specific to the R148 position causing loss of negative regulation for USP18, which normally restraints type 1 IFN signaling.
STAT3	AD, LOF, DN	Hyper-IgE syndrome Defective Th17 development
STAT3	AD, GOF	Bacterial (staph, strep), viral (HSV), and fungal (Candida) infections Multiple autoimmunity and IPEX-like phenotype Lymphoproliferation Growth failure Lymphopenia Reduced Treg cells Increased double-negative T-cells Increased IL-6 levels
STAT3	GOF, somatic	Large granular lymphocyte leukemia
STAT4	AD, LOF, DN	Paracoccidioidomycosis Decreased IL-12-induced IFN-γ response Decreased fungicidal activity
STAT4	Polymorphisms	Systemic lupus erythematosus Rheumatoid arthritis
STAT5B	AR, LOF	Viral infections, hemorrhagic varicella in some cases IPEX-like phenotype (eczema, thrombocytopenic purpura, lymphocytic interstitial pneumonitis) Growth failure (GH insensitive) Decreased Treg cells with high serum IgE levels
STAT5B	AD, LOF, DN	Growth failure Eczema High serum IgE levels
STAT5B	AD, GOF	Severe eczema Food allergies Eosinophilia and high serum IgE levels T-cell responses towards Th2 Elevated effector memory T-cells and Treg cells
STAT5B	GOF, somatic	Large granular lymphocyte leukemia
STAT6	AD, GOF	Severe eczema complicated with infections Food allergies Anaphylaxis Failure to thrive Eosinophilic gastrointestinal involvement Augmented p-STAT6 activity T-cell responses towards Th2
STAT6	GOF, somatic	Lymphoma

AD: Autosomal dominant, AR: Autosomal recessive, DN: Dominant negative, GOF: Gain-of-function, LOF: Loss-of-function, IPEX: Immune dysregulation, polyendocrinopathy X-linked, IFN: Interferon

patients with STAT1 and STAT3 GOF diseases (12,36), organ-specific autoimmunity has not been reported so far in STAT6 GOF disease. Also, the patients showed normal serum immunoglobulin levels with adequate antibody responses and T-cell activation and proliferation (17,20).

Precision Therapy of STAT6 GOF Disease by Targeting the JAK-STAT Pathway

Before its discovery, most patients with STAT6 GOF disease received systemic therapies including corticosteroids, methotrexate and mepolizumab, yielding limited to no relief from their symptoms. The identification of germline STAT6 GOF mutations in these patients opened the door to utilizing targeted therapies for achieving better disease control (37). Recently, data have been available on successfully using JAK inhibitors or anti-IL-4Rα antibodies in STAT6 GOF disease (17,20). Oral therapy with the JAK inhibitor ruxolitinib was initiated in our patient with a dose of 20 mg/m^2/daily. This therapy effectively controlled the skin manifestations, leading to a nearly normal appearance of the skin within one month of treatment initiation. Notably, this improvement was accompanied by the resolution of eosinophilic esophagitis-associated dysphagia and a successful catch-up in weight gain during the follow-up period. Importantly, the administration of ruxolitinib did not result in any drug-related adverse effects or infections over the course of the two-year treatment. Ruxolitinib therapy exerted notable control over blood eosinophil counts and led to a reduction in serum IgE levels. Furthermore, it normalized the decreased circulating naïve T cells and the elevated memory T-cells and Treg cells. Additionally, it decreased the Th2 skewing, as evidenced by reduced IL-4 and increased IL-17 and IFN-γ. Mechanistically, treatment with ruxolitinib effectively curtailed the activation of pSTAT6 in the patient's T cells both at baseline and following stimulation with IL-4 (17).

Sharma et al. (20) conducted *in vitro* investigations demonstrating the efficacy of both ruxolitinib and tofacitinib in effectively reducing the heightened phosphorylation of the mutant STAT6 proteins, both at baseline and following IL-4 stimulation as well as enhanced STAT6 dephosphorylation following cessation of IL-4 treatment. Treatment with the anti-IL-4Rα chain antibody Dupilumab also inhibited IL-4-mediated augmentation of STAT6 phosphorylation. Three patients were treated with Dupilumab, with one undergoing treatment for over a span of 2 years. All three individuals exhibited marked clinical responses characterized by the controlled management of atopic dermatitis and the discontinuation of systemic corticosteroid therapy. Additionally, one patient displayed a rapid increase in height and weight following treatment. Mechanistically, transcriptomic data confirmed the inhibitory effects of Dupilumab by showing decreased Th2 gene expression and decreased expression of IL-4Rα on both naive CD4$^+$ and CD8$^+$ T-cells. Another patient who received tofacitinib (5 mg/day) exhibited reduced dysphagia and food impaction, in association with improved upper GI endoscopy findings and reduced intraepithelial eosinophils. Collectively, these studies expand the potential applications of Jakinibs and Dupilumab in primary atopic disorders by establishing their efficacy in achieving disease control in STAT6 GOF disease. Nevertheless, the long-term outcomes of these targeted therapies remain obscure and necessitate further observational studies.

Conclusion

Mutations affecting STAT proteins have been systematically categorized along a spectrum, encompassing a wide range of immune response dysregulation. This spectrum spans from mutations leading to insufficient immune responses, which render individuals vulnerable to infections, to mutations resulting in excessive immune activation, contributing to autoimmune and hyperinflammatory conditions (Table 2). Within this spectrum of STAT-related disorders the recently identified STAT6 GOF disease further broadens our understanding of the functional diversity within the STAT family and provides fresh insights into the mechanisms behind this group of immune disorders. Overall, our own studies and those of other groups clearly demonstrate that patients with moderate to severe eczema and other recalcitrant allergic manifestations who are resistant to classical treatment approaches should be investigated for primary atopic diseases including STAT6 GOF disease. Further elucidating the underlying mechanisms of this novel primary atopic disorder their targeting by tailored precision therapies promise superior disease control and better long-term outcomes for the affected patients.

Authorship Contributions

Concept: S.B, T.C., Design: S.B, T.C., Literature Search: S.B, T.C., Writing: S.B, T.C.

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References

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42:1473-507.
2. Vaseghi-Shanjani M, Snow AL, Margolis DJ, Latrous M, Milner JD, Turvey SE, et al. Atopy as immune dysregulation: Offender genes and targets. J Allergy Clin Immunol Pract. 2022;10:1737-56.
3. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet. 1966;1:1013-5.

4. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007;448:1058-62.
5. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008;452:773-6.
6. Al Khatib S, Keles S, Garcia-Lloret M, Karakoc-Aydiner E, Reisli I, Artac H, et al. Defects along the T(H)17 differentiation pathway underlie genetically distinct forms of the hyper IgE syndrome. J Allergy Clin Immunol. 2009;124:342-8, 8 e1-5.
7. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med. 2009;206:1291-301.
8. Jabara HH, McDonald DR, Janssen E, Massaad MJ, Ramesh N, Borzutzky A, et al. DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. Nat Immunol. 2012;13:612-20.
9. Baris S, Alroqi F, Kiykim A, Karakoc-Aydiner E, Ogulur I, Ozen A, et al. Severe early-onset combined immunodeficiency due to heterozygous gain-of-function mutations in STAT1. J Clin Immunol. 2016;36:641-8.
10. Alroqi FJ, Charbonnier LM, Baris S, Kiykim A, Chou J, Platt CD, et al. Exaggerated follicular helper T-cell responses in patients with LRBA deficiency caused by failure of CTLA4-mediated regulation. J Allergy Clin Immunol. 2018;141:1050-9 e10.
11. Harb H, Stephen-Victor E, Crestani E, Benamar M, Massoud A, Cui Y, et al. A regulatory T cell Notch4-GDF15 axis licenses tissue inflammation in asthma. Nat Immunol. 2020;21:1359-70.
12. Kayaoglu B, Kasap N, Yilmaz NS, Charbonnier LM, Geckin B, Akcay A, et al. Stepwise reversal of immune dysregulation due to STAT1 gain-of-function mutation following ruxolitinib bridge therapy and transplantation. J Clin Immunol. 2021;41:769-79.
13. Kiykim A, Charbonnier LM, Akcay A, Karakoc-Aydiner E, Ozen A, Ozturk G, et al. Hematopoietic stem cell transplantation in patients with heterozygous STAT1 gain-of-function mutation. J Clin Immunol. 2019;39:37-44.
14. Kiykim A, Ogulur I, Dursun E, Charbonnier LM, Nain E, Cekic S, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. J Allergy Clin Immunol Pract. 2019;7:2790-800 e15.
15. Kolukisa B, Baser D, Akcam B, Danielson J, Bilgic Eltan S, Haliloglu Y, et al. Evolution and long-term outcomes of combined immunodeficiency due to CARMIL2 deficiency. Allergy. 2022;77:1004-19.
16. Cui Y, Benamar M, Schmitz-Abe K, Poondi-Krishnan V, Chen Q, Jugder BE, et al. A Stk4-Foxp3-NF-kappaB p65 transcriptional complex promotes T(reg) cell activation and homeostasis. Sci Immunol. 2022;7:eabl8357.
17. Baris S, Benamar M, Chen Q, Catak MC, Martinez-Blanco M, Wang M, et al. Severe allergic dysregulation due to a gain of function mutation in the transcription factor STAT6. J Allergy Clin Immunol. 2023;152:182-94 e7.
18. Suratannon N, Ittiwut C, Dik WA, Ittiwut R, Meesilpavikkai K, Israsena N, et al. A germline STAT6 gain-of-function variant is associated with early-onset allergies. J Allergy Clin Immunol. 2023;151:565-71 e9.
19. Takeuchi I, Yanagi K, Takada S, Uchiyama T, Igarashi A, Motomura K, et al. STAT6 gain-of-function variant exacerbates multiple allergic symptoms. J Allergy Clin Immunol. 2023;151:1402-9 e6.
20. Sharma M, Leung D, Momenilandi M, Jones LCW, Pacillo L, James AE, et al. Human germline heterozygous gain-of-function STAT6 variants cause severe allergic disease. J Exp Med. 2023;220.
21. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. Protein Sci. 2018;27:1984-2009.
22. Hou J, Schindler U, Henzel WJ, Ho TC, Brasseur M, McKnight SL. An interleukin-4-induced transcription factor: IL-4 Stat. Science. 1994;265:1701-6.
23. Levy DE, Darnell JE, Jr. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol. 2002;3:651-62.
24. Luo Y, Alexander M, Gadina M, O'Shea JJ, Meylan F, Schwartz DM. JAK-STAT signaling in human disease: From genetic syndromes to clinical inhibition. J Allergy Clin Immunol. 2021;148:911-25.
25. Toth KA, Schmitt EG, Cooper MA. Deficiencies and dysregulation of STAT pathways that drive inborn errors of immunity: Lessons from patients and mouse models of disease. J Immunol. 2023;210:1463-72.
26. Souza PP, Palmqvist P, Lundberg P, Lundgren I, Hanstrom L, Souza JA, et al. Interleukin-4 and interleukin-13 inhibit the expression of leukemia inhibitory factor and interleukin-11 in fibroblasts. Mol Immunol. 2012;49:601-10.
27. Dagoneau N, Scheffer D, Huber C, Al-Gazali LI, Di Rocco M, Godard A, et al. Null leukemia inhibitory factor receptor (LIFR) mutations in Stuve-Wiedemann/Schwartz-Jampel type 2 syndrome. Am J Hum Genet. 2004;74:298-305.
28. Nieminen P, Morgan NV, Fenwick AL, Parmanen S, Veistinen L, Mikkola ML, et al. Inactivation of IL11 signaling causes craniosynostosis, delayed tooth eruption, and supernumerary teeth. Am J Hum Genet. 2011;89:67-81.
29. Yildiz M, Li H, Bernard D, Amin NA, Ouillette P, Jones S, et al. Activating STAT6 mutations in follicular lymphoma. Blood. 2015;125:668-79.
30. Minskaia E, Maimaris J, Jenkins P, Albuquerque AS, Hong Y, Eleftheriou D, et al. Autosomal dominant STAT6 gain of function causes severe atopy associated with lymphoma. J Clin Immunol. 2023;43:1611-22.
31. Kuperman D, Schofield B, Wills-Karp M, Grusby MJ. Signal transducer and activator of transcription factor 6 (Stat6)-deficient mice are protected from antigen-induced airway hyperresponsiveness and mucus production. J Exp Med. 1998;187:939-48.
32. Tomkinson A, Kanehiro A, Rabinovitch N, Joetham A, Cieslewicz G, Gelfand EW. The failure of STAT6-deficient mice to develop airway eosinophilia and airway hyperresponsiveness is overcome by interleukin-5. Am J Respir Crit Care Med. 1999;160:1283-91.
33. Mikita T, Daniel C, Wu P, Schindler U. Mutational analysis of the STAT6 SH2 domain. J Biol Chem. 1998;273:17634-42.
34. Daniel C, Salvekar A, Schindler U. A gain-of-function mutation in STAT6. J Biol Chem. 2000;275:14255-9.
35. Tachdjian R, Al Khatib S, Schwinglshackl A, Kim HS, Chen A, Blasioli J, et al. In vivo regulation of the allergic response by the IL-4 receptor alpha chain immunoreceptor tyrosine-based inhibitory motif. J Allergy Clin Immunol. 2010;125:1128-36 e8.
36. Leiding JW, Vogel TP, Santarlas VGJ, Mhaskar R, Smith MR, Carisey A, et al. Monogenic early-onset lymphoproliferation and autoimmunity: Natural history of STAT3 gain-of-function syndrome. J Allergy Clin Immunol. 2023;151:1081-95.
37. Giancotta C, Colantoni N, Pacillo L, Santilli V, Amodio D, Manno EC, et al. Tailored treatments in inborn errors of immunity associated with atopy (IEIs-A) with skin involvement. Front Pediatr. 2023;11:1129249.