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STAT3: A year in Review

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Summary

The discovery of new gain of function mutations in STAT3, as well as new studies among patients with loss of function mutations, expand the understanding of the pathophysiology of STAT3 function and its importance in regulating the immune system. These findings contribute to elucidating STAT3 biology and clinical symptoms in patients with the different disease phenotypes.

Keywords

STAT3; Autoimmunity; Lymphoproliferation; Immunodeficiency; Th17 cells; Job's syndrome

Introduction

STAT3 is an important transcription factor that transmits signals to the nucleus after cytokine stimulation. After cytokine stimulation, the Janus Kinase (JAK) phosphorylates the cytokine receptor which activates cytokine receptor-associated kinases which tyrosine-phosphorylate STATs. Then, two STAT molecules homo- or hetero-dimerize via their SH2 domain and translocate to the nucleus to bind to specific DNA elements to regulate gene expression. (1) STAT3 promotes and regulates the transcription of target genes involved in proliferation, apoptosis, and differentiation (2). STAT3 is important in modulating both innate and adaptive responses through several cytokines including IFNs, IL-2, IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27 (3). Dominant negative loss of function mutations in STAT3 cause the autosomal dominant Hyper IgE syndrome (AD-HIES or Job's syndrome) characterized by recurrent bacterial lung and skin infections associated

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with cold abscess formation, severe eczematoid rash, chronic mucocutaneous candidiasis, primary structural connective tissue abnormalities and arterial tortuosity/aneurysm formation. This loss of function does not correspond to a complete absence of the protein or of its function as the complete absence of STAT3, has not been seen in humans, and is lethal in mice (4). Homo-dimerization of the wild-type protein allows for a residual function of about 20–30%. Gain of STAT3 function has classically been associated with neoplasms (5) while specific somatic mutations in STAT3 have been reported in a large subset of LGL patients (6). Studying patients with STAT3 mutations continues to reveal critical biological pathways in which STAT3 participates, and how they affect normal human function as well as disease. The purpose of this review is to report the recent literature on STAT3 germline diseases and the effects on the immune system.

Candidiasis, bacterial infection and abnormal IL-17-producing cells in patients with STAT3 loss of function

STAT3 mutations in AD-HIES were first reported in 2007. Since then, a number of fundamental findings regarding STAT3 function in a variety of immunologic and non-immunologic pathways have been revealed as a direct result of the study of these patients (7, 8). One of the first such observations was that the patients, whose only common fungal disease was mucocutaneous candidiasis, lacked to capacity to generate IL-17 producing T-cells and normally upregulate ROR-γt, the master transcription factor for Th17 cells (9–12). Subsequent work studying genes directly in the IL-17 pathway has borne out that IL-17, a fundamental cytokine in T-helper biology, appears be responsible largely just for host defense against candidiasis and perhaps some staph infection, which is also seen in AD-HIES. More recently patients with loss-of function mutations in *RORC*, the gene which encodes RORγt in humans, were described (13). Interestingly, in addition to the expected inability to generate Th17 cells and resultant candidiasis, the patients also failed to mount a normal IFNγ response to mycobacteria, leading to opportunistic mycobacterial infection. (13). This was a surprising finding given that no such defect or infectious predilection is seen in AD-HIES despite the impaired capacity for RORγt upregulation(14). This observation might be partially explained by the recent finding that while unconventional T cells (which could have roles in anti-mycobacterial immunity) such as natural killer T cells (NKT cells) and mucosal-associated invariant T cells (MAIT cells) are reduced in AD-HIES, the MAIT at least express normal levels of ROR γt(15).

Viral reactivation and antibody defects: Impact of STAT3 on T-cell memory, T-cell and NK cell cytotoxicity and B-cell help

Patients with HIES have an increased rate of reactivation of chronic herpesvirus infections, EBV and VZV in particular(16, 17). This susceptibility was though to be at least in part due to a reduction in central memory CD4+ T-cells in AD-HIES (16, 17). In addition, the cytokine IL-21, which can activate STAT3, was shown to be critical for CD8+ T cell function *in vitro* and increase survival and proliferation of mouse central memory CD8+ T cells(18). It induces important effector molecules in CD8+ T cells such as IFN-γ, granzyme B and perforin (19–22). Ives et al (23) used the AD-HIES model to study the effects of IL-21 on STAT3 signaling on the homeostasis and function of human CD8+ effector T cells, finding a decrease in central and effector memory T cell numbers in the STAT3 deficient

patients. More intriguingly, STAT3 signaling appeared to be critical for certain forms of CD8 and NK mediated cytotoxicity. NKG2D is an activating receptor that plays a critical role in the immune response mediated by NK cells to viral infections(24). STAT3 activation through IL-21 stimulation increases the expression of NKG2D in NK cells, which is lower in conditional STAT3 deletion and NK cells of AD-HIES patients(25). Therefore, it is possible that the viral reactivation defect in STAT3 deficient patients may be affected by abnormalities in CD8+ T cell and NK cell viral defense; although of interest, primary viral infections are not particularly pathogenic in AD-HIES (23).

The abnormal B cell function and antibody responses in AD-HIES are likely due to the role for STAT3 in follicular T cell (Tfh) differentiation and IL-21 signaling in naïve B cell differentiation.(11, 26). Although memory B cell levels are decreased, antibody levels are largely normal in AD-HIES, likely attributable to the observation that the few circulating B cells found in these patients are capable of differentiating into antibody-secreting plasma cells suggesting a STAT 3 independent plasma cell differentiation pathway (27).

STAT 3 and Allergy

STAT3 deficient patients have an increased level of IgE but paradoxically appear to be relatively protected from atopic disease(28, 29). In that regard, AD-HIES patients stand in stark contrast to other genetic diseases associated with infection and marked IgE elevation, such as DOCK8 and PGM3 deficiencies. One observed mechanism appears to be a relative impairment of mast cell and basophil degranulation in the context of STAT3 mutations(28). There may also be a role for STAT3 in generating allergen-specific IgE. While Siegel et al saw elevated levels of food allergen-specific IgE(28), Boos et al saw no increase in allergen-specific IgE to a large variety of allergens or nor any increased skin prick test positivity compared to non-atopic controls (29).

Increased STAT3 function in and autoimmunity and lymphoproliferation

Stat3 function has been linked to increased cell survival and autoimmunity in a variety of experimental models(3, 30–32). Somatic activating gain-of-function (GOF) STAT3 mutations in the SH2 domain have been described in patients with T cell and NK cell Large Granular Cell Leukemia characterized by adult-onset lymphoproliferation, as well as autoimmunity with immune-mediated cytopenias. (6, 33) Genome wide association studies (GWAS) have also linked a STAT3 polymorphism to inflammatory bowel disease (IBD) (34, 35). Additionally, in a meta-analysis of ulcerative colitis and crohn’s disease GWAS with 75,000 cases and controls, there was overlap with IBD loci, including STAT3, and mycobacterial disease(36).

It is in that context that several groups recently identified a syndrome of early onset autoimmunity and lymphoproliferation with highly variable penetrance and presentation in 19 individuals with germline heterozygous STAT3 mutations (Table 1)(37–40). In contrast to AD-HIES patients, the mutations in these cohorts resulted in gain of transcriptional activity assessed with a dual-luciferase reporter assay(37, 39). Patients presented with a wide spectrum of lymphoproliferative and autoimmune disease including enteropathy, lymphocytic interstitial lung disease and autoimmune cytopenias, associated with growth

delay, endocrinopathies (diabetes), hepatic dysfunction, and susceptibility to opportunisitic infections including mycobacterial disease. Among these 19 patients, the clinical manifestations are very diverse: Early-onset type 1 diabetes (n=6); short stature (n=12); autoimmune cytopenias (n=14); lymphadenopathy (n=11); lymphoproliferation (n=10); intestinal manifestations (n = 9) including enteropathy (n=6), celiac disease (n=2) and nonspecific colitis (n = 1); cutaneous manifestations (n = 9) including eczema (n=6), alopecia (n=2) and non specific dermatitis (n=1); autoimmune lung disease (n=6); arthritis (n=3); and uveitis (n=1). All patients in Haapaniemi's cohort presented with hypogammaglobulinemia, associated with decreased switched memory B cells, NK cells and plasmacytoid dendritic cells. In Milner's cohort, 5 patients had hypogammaglobulinemia, 3 had a T cell lymphopenia and one had B cell lymphopenia. A majority of patients presented with recurrent infections (n =11), including fungal infections (39)and mycobacteria infection (38). Hypogammaglobulinemia with terminal B-cell maturation arrest, dendritic cell deficiency, variable Th17 cell numbers as well as low circulating eosinophils were observed as well(38, 39).

Many of the observed immune abnormalities were consistent with increased STAT3 activity leading to suppression of other STAT pathways. Milner et al reported decreased T regulatory cells and impaired STAT5 activation reminiscent of patients with loss of function STAT5b who have numerous overlapping symptoms with gain of function STAT3 patients including short stature, enteropathy, cytopenias, lymphocytic interstitial lung disease, and endocrinopathies(41). They also found diminished STAT1 phosphorylation, which could potentially account for other immune regulatory defects, as well as the mycobacterial disease observed in a subset of the patients (39). The STAT1/STAT5 defects may be explained by increased expression of suppressor of cytokine signaling 3 (SOCS3), a STAT3 target which also serves as a negative regulator of STAT3 (42) STAT1 and STAT5 (42). The precise etiology of the observed infections is difficult to ascertain since most of the patients have been on chronic immune suppression, however the antibody defects as well as some of the cellular defects were observed in a handful of patients off immune suppression as well. Immunosuppression was key to therapeutic intervention in these patients. Blocking IL-6 activation with tocilizumab in one patient resulted in a dramatic improvement in arthritis and a reduction of TH-17 numbers to normal levels. Hematopoietic stem cell transplantation (HSCT) was performed in two patients; one was curative in one patient with complete resolution of autoimmune symptoms and the other patient died of adenovirus infection and refractory graft vs. host disease(39, 40). Surprisingly, despite the connection between increased STAT3 activity and neoplastic disease, as well as the observation that somatic GOF mutations in STAT3 lead to LGL, neoplastic disease was quite rare in the cohorts reported. One patient developed T-cell large granular lymphocytic leukemia at age 14 (38).

Conclusion

Studying patients with STAT3 loss of function in AD-HIES and gain of function in the lymphoproliferative STAT3 disease, we gain key insights into the role STAT3 plays in regulation of the immune system. The wide range of phenotypes demonstrates the diversity of function of STAT3 in the immune system and its tight regulation. Further examination of

these disorders will continue to reveal both the cellular consequences of disturbing such regulation, as well as the clinical manifestations.

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References

1. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. The New England journal of medicine. 2013 Jan 10; 368(2):161–70. [PubMed: 23301733]
2. Villarino AV, Kanno Y, Ferdinand JR, O'Shea JJ. Mechanisms of Jak/STAT signaling in immunity and disease. Journal of immunology. 2015 Jan 1; 194(1):21–7.
3. Harris TJ, Grosso JF, Yen HR, Xin H, Kortylewski M, Albesiano E, et al. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. Journal of immunology. 2007 Oct 1; 179(7):4313–7.
4. Takeda K, Noguchi K, Shi W, Tanaka T, Matsumoto M, Yoshida N, et al. Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality. Proceedings of the National Academy of Sciences of the United States of America. 1997 Apr 15; 94(8):3801–4. [PubMed: 9108058]
5. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nature reviews Cancer. 2014 Nov; 14(11):736–46. [PubMed: 25342631]
6. Koskela HL, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmaki H, Andersson EI, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. The New England journal of medicine. 2012 May 17; 366(20):1905–13. [PubMed: 22591296]
7. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. The New England journal of medicine. 2007 Oct 18; 357(16):1608–19. [PubMed: 17881745]
8. 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 Aug 30; 448(7157):1058–62. [PubMed: 17676033]
9. 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 Apr 10; 452(7188):773–6. [PubMed: 18337720]
10. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. The Journal of experimental medicine. 2008 Jul 7; 205(7):1543–50. [PubMed: 18591412]
11. Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. The Journal of experimental medicine. 2008 Jul 7; 205(7):1551–7. [PubMed: 18591410]
12. Renner ED, Rylaarsdam S, Anover-Sombke S, Rack AL, Reichenbach J, Carey JC, 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. The Journal of allergy and clinical immunology. 2008 Jul; 122(1):181–7. [PubMed: 18602572]
13•. Okada S, Markle JG, Deenick EK, Mele F, Averbuch D, Lagos M, et al. Impairment of immunity to Candida and Mycobacterium in humans with bi-allelic RORC mutations. Science. 2015 Jul 9. Describes a new immunodeficiency in which patients fail to generate Th17 cells or mount a proper response to IFN-γ.

14•. Bandaru A, Devalraju KP, Paidipally P, Dhiman R, Venkatasubramanian S, Barnes PF, et al. Phosphorylated STAT3 and PD-1 regulate IL-17 production and IL-23 receptor expression in Mycobacterium tuberculosis infection. European journal of immunology. 2014 Jul; 44(7):2013–24. PD-1 and STAT3 regulation is important for IL-17 and IL-23 production. Increased PD-1, decreased STAT3 phosphorylation and decreased production of IL-17 and IL-23 are seen in Tuberculosis patients compared to healthy controls. [PubMed: 24643836]

15••. Wilson RP, Ives ML, Rao G, Lau A, Payne K, Kobayashi M, et al. STAT3 is a critical cell-intrinsic regulator of human unconventional T cell numbers and function. The Journal of experimental medicine. 2015 Jun 1; 212(6):855–64. Unconventional T cells such as MAIT and NKT cells are decreased in AD-HIES patients. These cells are implicated in candidal and *Staph aureus* defense which is impaired in AD-HIES. STAT3 is important in downstream signaling of IL-21 and IL-23 receptors for production and survival of unconventional T cells. [PubMed: 25941256]

16. Siegel AM, Heimall J, Freeman AF, Hsu AP, Brittain E, Brenchley JM, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. Immunity. 2011 Nov 23; 35(5):806–18. [PubMed: 22118528]

17. Chandesris MO, Melki I, Natividad A, Puel A, Fieschi C, Yun L, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. Medicine. 2012 Jul; 91(4):e1–19. [PubMed: 22751495]

18. Cui W, Liu Y, Weinstein JS, Craft J, Kaech SM. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. Immunity. 2011 Nov 23; 35(5):792–805. [PubMed: 22118527]

19. Ichii H, Sakamoto A, Hatano M, Okada S, Toyama H, Taki S, et al. Role for Bcl-6 in the generation and maintenance of memory CD8+ T cells. Nature immunology. 2002 Jun; 3(6):558–63. [PubMed: 12021781]

20. Parmigiani A, Pallin MF, Schmidtmayerova H, Lichtenheld MG, Pahwa S. Interleukin-21 and cellular activation concurrently induce potent cytotoxic function and promote antiviral activity in human CD8 T cells. Human immunology. 2011 Feb; 72(2):115–23. [PubMed: 20977918]

21. Strengell M, Sareneva T, Foster D, Julkunen I, Matikainen S. IL-21 up-regulates the expression of genes associated with innate immunity and Th1 response. Journal of immunology. 2002 Oct 1; 169(7):3600–5.

22. Zeng R, Spolski R, Casas E, Zhu W, Levy DE, Leonard WJ. The molecular basis of IL-21-mediated proliferation. Blood. 2007 May 15; 109(10):4135–42. [PubMed: 17234735]

23. Ives ML, Ma CS, Palendira U, Chan A, Bustamante J, Boisson-Dupuis S, 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. The Journal of allergy and clinical immunology. 2013 Aug; 132(2):400–11e9. [PubMed: 23830147]

24. Ogasawara K, Lanier LL. NKG2D in NK and T cell-mediated immunity. Journal of clinical immunology. 2005 Nov; 25(6):534–40. [PubMed: 16380817]

25••. Zhu S, Phatarpekar PV, Denman CJ, Senyukov VV, Somanchi SS, Nguyen-Jackson HT, et al. Transcription of the activating receptor NKG2D in natural killer cells is regulated by STAT3 tyrosine phosphorylation. Blood. 2014 Jul 17; 124(3):403–11. AD-HIES and conditional knock out NK cells have lower NKG2D expression and blunted reponses to IL-10 and IL-21. STAT3 does bind to a predicted binding site upstream of NKG2D. These data suggest STAT3 is important for NKG2D expression upon cytokine stimulation. [PubMed: 24891320]

26. Avery DT, Ma CS, Bryant VL, Santner-Nanan B, Nanan R, Wong M, et al. STAT3 is required for IL-21-induced secretion of IgE from human naive B cells. Blood. 2008 Sep 1; 112(5):1784–93. [PubMed: 18579794]

27. Deenick EK, Avery DT, Chan A, Berglund LJ, Ives ML, Moens L, et al. Naive and memory human B cells have distinct requirements for STAT3 activation to differentiate into antibody-secreting plasma cells. The Journal of experimental medicine. 2013 Nov 18; 210(12):2739–53. [PubMed: 24218138]

28. Siegel AM, Stone KD, Cruse G, Lawrence MG, Olivera A, Jung MY, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell

degranulation. The Journal of allergy and clinical immunology. 2013 Dec; 132(6):1388–96. [PubMed: 24184145]

29••. Boos AC, Hagl B, Schlesinger A, Halm BE, Ballenberger N, Pinarci M, et al. Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. Allergy. 2014 Jul; 69(7):943–53. This study compared the presense of atopy with elevated IgE in STAT3 and DOCK8 patients. Specific IgE in AD-HIES is not elevated to a variety of allergens despite elevated total IgE. Whereas, DOCK8 patients have significant atopy associated with the elevated IgE. [PubMed: 24898675]

30. Laurence A, Amarnath S, Mariotti J, Kim YC, Foley J, Eckhaus M, et al. STAT3 transcription factor promotes instability of nTreg cells and limits generation of iTreg cells during acute murine graft-versus-host disease. Immunity. 2012 Aug 24; 37(2):209–22. [PubMed: 22921119]

31. Durant L, Watford WT, Ramos HL, Laurence A, Vahedi G, Wei L, et al. Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis. Immunity. 2010 May 28; 32(5):605–15. [PubMed: 20493732]

32. de Koning JP, Soede-Bobok AA, Ward AC, Schelen AM, Antonissen C, van Leeuwen D, et al. STAT3-mediated differentiation and survival and of myeloid cells in response to granulocyte colony-stimulating factor: role for the cyclin-dependent kinase inhibitor p27(Kip1). Oncogene. 2000 Jul 6; 19(29):3290–8. [PubMed: 10918585]

33. Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012 Oct 11; 120(15):3048–57. [PubMed: 22859607]

34. Franke A, Balschun T, Karlsen TH, Hedderich J, May S, Lu T, et al. Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. Nature genetics. 2008 Jun; 40(6):713–5. [PubMed: 18438405]

35. Willson TA, Kuhn BR, Jurickova I, Gerad S, Moon D, Bonkowski E, et al. STAT3 genotypic variation and cellular STAT3 activation and colon leukocyte recruitment in pediatric Crohn disease. Journal of pediatric gastroenterology and nutrition. 2012 Jul; 55(1):32–43. [PubMed: 22197944]

36. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012 Nov 1; 491(7422):119–24. [PubMed: 23128233]

37••. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Lango Allen H, De Franco E, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nature genetics. 2014 Aug; 46(8):812–4. In this report, the authors present the first series of patients with STAT3 GOF disease. These patients present with germline mutations in STAT3 which cause multi-organ autoimmune disease including type 1 diabetes and short stature. [PubMed: 25038750]

38•. Haapaniemi EM, Kaustio M, Rajala HL, van Adrichem AJ, Kainulainen L, Glumoff V, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood. 2015 Jan 22; 125(4):639–48. This study reports 3 cases with STAT3 GOF disease (1 new and 2 reported in Flanagan et al) with the autoimmune features as well as severe mycobacterial infection. [PubMed: 25349174]

39••. Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pedersen A, Niemela JE, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood. 2015 Jan 22; 125(4):591–9. This study expands the phenotype for STAT3 GOF patients by presenting 13 patients in 10 families with significant early-onset lymphoproliferation, autoimmune disease and immunodeficiency. This group went on to explore the mechanism which includes abnormal STAT1/STAT5 activity with decreased Tregs and increased SOCS3 expression. [PubMed: 25359994]

40. Haddad E. STAT3: too much may be worse than not enough! Blood. 2015 Jan 22; 125(4):583–4. [PubMed: 25614633]

41. Kanai T, Jenks J, Nadeau KC. The STAT5b Pathway Defect and Autoimmunity. Frontiers in immunology. 2012; 3:234. [PubMed: 22912632]

42. Carow B, Rottenberg ME. SOCS3, a Major Regulator of Infection and Inflammation. Frontiers in immunology. 2014; 5:58. [PubMed: 24600449]

Purpose of this review

Signal Transducer and Activator of Transcription 3 (STAT3) is an important transcription factor involved in a wide variety of cellular functions. Germline loss of function mutations are known to cause Hyper-IgE immunodeficiency (AD-HIES), while somatic gain of function (GOF) mutations have been described in Large granular cell leukemia, and polymorphisms in STAT3 have been associated with IBD and other solid organ tumors. The review examines recent discoveries in our understanding of the non-malignant disease processes affected by STAT3 mutations in human disease.

Recent Findings

Germline STAT 3 GOF mutations have recently been identified in patients with an early-onset autoimmunity/lymphoproliferative syndrome. STAT3 plays a previously unrecognized role in several facets of the pathogenesis of allergy. Loss of function STAT3 mutations revealed critical roles for STAT3 in the development and function of several lymphocyte populations and in their role in host defense.

Key Points

1. The study of AD-HIES has significantly increased our knowledge of the diverse functions of STAT3 in the immune system.
2. STAT3 plays a role in regulation of T cell subsets as well as mast cells and NK cells.
3. Gain of function of STAT3 leads to an early onset autoimmune disease characterized by immunodeficiency and lymphoproliferation.
4. The study of new disease phenotypes in known genes leads to discovery of novel disease pathways.

Table 1

Table 1	Inheritance	Clinical presentation	Laboratory findings	Reference
STAT3 LOF	Germline AD	• Mucocutaneous candidiasis, • Pneumonia (*S. aureus*, *S. pneumonia*), • Pneumatoceles, • Dermatitis, • Connective tissue and bone abnormalities.	↑ IgE ↓ TH17 ↓ T follicular help ↓ B-cell maturation and function ↓ mast cell degranulation ↓ NK cell activation ↓ CD8+ function	1,7,8,23,25,27,28,40
STAT 3 GOF	Germline AD	• ALPS-like • IPEX-like • STAT5b deficiency-like • Multi-organ Autoimmunity • Infections • Immune deficiency: hypo-IgG, reduced memory B cells	↑ IL-6 signaling ↓ SOCS3 ↓ pSTAT5 ↓ pSTAT1 ↓ Tregs	37–40
STAT 3 LGL	Somatic AD	• Autoimmunity • Cytopenias • Multi-organ lymphoproliferative disease	↓ SOCS1 ↑ JAK2 RNA Peripheral LGL expansion (0.5×10^9/L) +LGL on BM biopsy/aspirate T cell LGL: ○ Activated T cells by Flow cytometry (FACS) CD3+CD8+CD57+ ○ Clonality by TCRγ PCR and/or Vβ by FACS NK cell LGL: ○ Activated NK cells by FACS (CD3-CD56+CD8+CD16+/−) ○ KIR expression by FACS	1, 6, 33