

Pathogenesis of Hyper IgE Syndrome

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Abstract Hyper IgE syndrome (HIES) is a rare primary immunodeficiency characterized by the triad of elevated IgE and eosinophilia, eczema, and recurrent skin and pulmonary infections. The autosomal dominant (AD) form of HIES results from mutations in *STAT3* and is characterized by disordered inflammation, connective tissue, and skeletal abnormalities. Tissue-specific *STAT3* deficiency in animals, cytokine and transcriptional array data, and careful clinical phenotyping have explained some of the pathophysiology of the immunologic and non-immunologic abnormalities of AD-HIES. In depth study of the role of *STAT3* mutations in specific aspects of HIES may lead to better understanding and new approaches to treatment of conditions intrinsic to HIES that are common in the general population, such as staphylococcal infections, scoliosis, osteoporosis, bronchiectasis, and arterial aneurysms. As the genotypes of *STAT3* deficiency are further characterized, genotype–phenotype correlations may emerge that will be informative regarding specific molecular interactions. Autosomal recessive forms of hyper IgE (AR-HIES) have also been reported. A single case of homozygous deficiency of the signal protein Tyk2 has been reported as well as a recessive syndrome with some features overlapping AD-

HIES, but for which the genetic etiology is unknown. Better understanding of the pathophysiology and mechanisms of dominant and recessive hyper IgE syndromes will shed light on somatic and immune biology and may improve quality of life and survival for HIES patients.

Keywords Hyper IgE syndrome · *STAT3* · Autosomal dominant · IL-17 · Scoliosis · Aneurysms

Introduction

Autosomal dominant Hyper IgE syndrome (HIES) was first described as Job's syndrome in 1966 and included the triad of eosinophilia, eczema, and recurrent skin and pulmonary infections [1]. IgE was recognized as a cardinal feature in 1972 and the name hyper IgE syndrome was proposed [2]. The phenotype was later expanded to include many connective tissue and skeletal abnormalities [3, 4]. Dominant negative mutations in the signal transduction and activation of transcription (STAT) 3 gene account for the vast majority of autosomal dominant (AD) and sporadic cases, but the pathogenesis of some of the varied clinical features of HIES remains poorly understood [5, 6]. In this review, we will discuss the clinical phenotype, genetic features, and immunology of HIES, and discuss animal models of *STAT3* deficiency. In addition, we will briefly discuss the autosomal recessive forms of HIES.

Autosomal dominant and sporadic *STAT3* deficiency

Patients with HIES experience severe recurrent cutaneous and pulmonary infections with modest systemic signs of inflammation. The patients experience pneumonia starting in early

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childhood due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [3, 4]. Even when treated aggressively and promptly, the pneumonias often progress to pneumatocele formation, presumably due to dysregulated local inflammation and resultant tissue destruction. Superinfection of the pneumatoceles with *Pseudomonas aeruginosa* and molds such as *Aspergillus* and *Scedosporium* can be associated with significant morbidity and mortality [7]. Eczematoid dermatitis starts in the newborn period and is typically associated with and driven by *S. aureus* infection [8, 9]. Skin abscesses due to *S. aureus* are common and typically not associated with a robust inflammatory response either locally or systemically, hence the term “cold abscesses”. Mucocutaneous candidiasis, including onychomycosis, occurs frequently. Opportunistic infections including *Pneumocystis jiroveci* pneumonia, disseminated histoplasmosis, and cryptococcal infections also occur, although less frequently [10–12].

AD-HIES is also associated with multiple connective tissue and skeletal abnormalities including scoliosis, hyperextensibility, pathologic fractures, retained primary dentition, craniosynostosis, and vascular abnormalities [3, 4]. Individuals share a characteristic facial appearance, with a broad nose, deep set eyes with prominent forehead, and generalized coarsening of the facial features with age. Scoliosis $>10^\circ$ is seen in 75% of patients, typically appearing during adolescence [4]. Many patients have hyperextensibility of at least one joint and as adults may develop degenerative joint disease. Retention of primary teeth is due to failure of primary tooth deciduation; characteristic palatal, tongue, and oral mucosal changes are often present as well [13, 14]. Minimal trauma fractures occur as well as osteoporosis, although these two findings appear to be independent of each other. Vascular abnormalities, including intracranial aneurysms and coronary artery ectasia, tortuosity, and aneurysms are common [15, 16]. Asymptomatic cerebral T2-weighted hyperintensities, increased prevalence of lacunar infarcts, and increased Arnold Chiari I malformations are seen on the brain MRIs of many patients [17–19].

The serum IgE is typically highly elevated ($>2,000$ IU/mL) while other immunoglobulins are generally normal. IgE normalizes in adulthood in about 20% of cases. Eosinophilia usually accompanies the IgE elevation but is not correlated with it [4].

Clinical diagnosis has been based on a profile of immunologic and non-immunologic features leading to a composite score that correlates reasonably well with identifying *STAT3* mutations [20]. The prevalence of these features is summarized in Table 1.

Mortality

Infections leading to fatal hemoptysis or fatal intracranial infection have been reported due to *P. aeruginosa*,

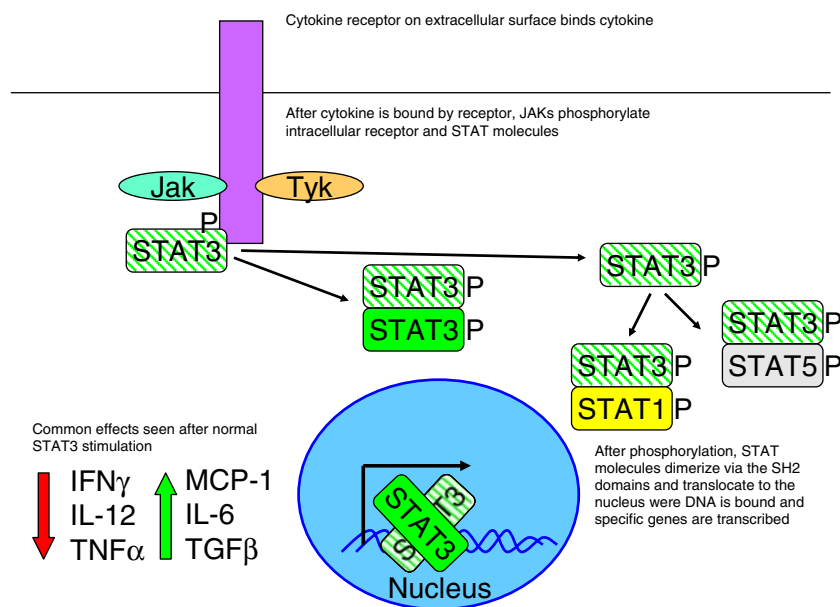
Table 1 Approximate prevalence of clinical features associated with HIES

Mean highest serum IgE (IU/mL) 15,920 ($n=63$ patients)	Mean highest eosinophils ($\#/\mu\text{L}$) 1,162 ($n=63$ patients)
Lifetime pneumonias (X-ray proven) 70% have >2	Scoliosis ($>10^\circ$) 60%
Parenchymal lung abnormalities (bronchiectasis/pneumatocele) 70%	Minimal trauma fractures (>1) 65%
Skin abscesses 75% have >4	Hyperextensibility 70%
Fatal infections 10%	Characteristic facies 85%
Recurrent sinusitis or otitis 80%	Retained primary teeth 70%
Candidiasis (oral/vaginal, fingernail, systemic) oral/vaginal 30%; fingernail 50%	Newborn rash 80%
Coronary vasculature anomalies 60%	Moderate–severe eczema 95%
Arnold Chiari I malformations 40%	Lymphoma 5%
Focal hyperintensities on brain MRI 75%	

Aspergillus fumigatus, and *Scedosporium prolificans*. These infections are secondary opportunists in post-infectious pneumatoceles and severe bronchiectasis [7]. Although there is significant inflammatory infiltrate of eosinophils, macrophages, and lymphocytes, minimal fibrosis is found surrounding the cavities and fungal invasion into local vasculature can cause fatal pulmonary hemorrhage [7]. HIES patients are at increased for Hodgkin's and Non-Hodgkin's Lymphoma (relative risk = 259), although the number of cases reported was small [21].

STAT3 mutations in HIES patients

Mutations in *STAT3* have been identified in most cases of autosomal dominant HIES [5, 6]. *STAT3* is one of seven STAT proteins in humans. The JAK-STAT pathway transduces signal for many cytokine receptors, leading to gene transcription and translation [22] (Fig. 1). The STAT proteins typically bind to JAKs, which are tyrosine kinases associated with the intracellular portions of cytokine receptors. When an appropriate cytokine binds to its cognate receptor, JAK phosphorylates the cytokine receptor and subsequently the STAT protein. The STAT then dissociates from the JAK-receptor complex and homo- or hetero-dimerizes within the cytosol via the phosphotyrosine and SRC homology 2 (SH2) domains. The dimerized STATs then translocate to the nucleus, bind the promoter sequences of target genes, and activate transcription. This activity is stopped by STAT dephosphorylation [22]. *STAT3* is located on human chromosome 17q21 and is activated in response to numerous cytokines, hormones, and growth factors. Gain of function mutations lead to inappropriate

Fig. 1 Cytokines and JAK-STAT signaling

activity in several malignancies including carcinoma of breast and prostate, multiple myeloma, leukemia, and lymphoma.

HIES-causing mutations in *STAT3* are predominantly missense and in-frame deletions that lead to production of protein with dominant negative activity [5, 6]. No null alleles have been identified to date, indicating that haploinsufficiency is not a mechanism for disease causation. This is consistent with the mouse data, which show that heterozygous *STAT3* deficiency is not associated with disease, while *STAT3* null animals die during embryogenesis. Taken together these data suggest that HIES patients have less than 50% *STAT3* activity, but clearly enough to sustain life and many aspects of development. The HIES *STAT3* mutations are located predominantly in the SH2, transactivation and DNA binding regions of *STAT3* [23]. HIES-causing *STAT3* mutations have been found in Asians, Africans, and Caucasians and correlate well with HIES disease. Currently, there are no clear correlations between phenotype and the affected region of *STAT3*. However, as more cases are reported and characterized subtle genotype–phenotype correlations may emerge.

Normal *STAT3* expression and trafficking to the nucleus is seen in HIES patients but the effector functions of *STAT3* are not normal [5, 6]. Some SH2 mutations cause defective *STAT3* phosphorylation despite IL-6 stimulation [23]. Mutations in the *STAT3* DNA-binding domain cause defective IL-6 and IL-10 signaling due to poor binding of target DNA and subsequent activation of relevant promoter sequences [6]. Laboratory constructs of specific DNA-binding domain mutations show that the DNA-binding activity is not completely inhibited but is about 25% of normal after stimulation [6]. When mutant *STAT3* was

expressed alongside the normal allele, as is the case in patients, IL-6 and IL-10 responses were repressed, demonstrating the dominant negative effect of the mutation [6].

Immunophenotype of HIES

The immunophenotype of HIES has long implicated defects in both innate and adaptive immune responses, leading to the suspicion that cytokines and chemokines, which are involved in all aspects of the immune response, were likely to be involved in the pathogenesis of HIES.

Cytokines, chemokines, and toll-like receptors

Cytokines are produced in response to diverse cellular stimuli and serve as growth factors and regulators of the immune response [24]. They act on multiple cell types with significant redundancy in their actions. Some cytokines associated with innate immunity are produced in response to activation of toll-like receptors (TLRs), receptors found on dendritic cells, phagocytes, endothelial cells, and others of the somatic and immune systems. TLRs recognize patterns such as those formed by lipid, carbohydrate, peptide, and nucleic acid structures. TLR signaling typically leads to activation of NF- κ B and expression of proinflammatory cytokines, chemokines, and endothelial adhesion molecules, thus guiding and augmenting the inflammatory response. Distinct cytokines control adaptive immunity through the stimulation of cognate receptors.

HIES is a disease of both too little and too much inflammatory response, which is in part explained by the important role of *STAT3* in the regulation of key cytokines,

including IL-6, IL-10, IL-17, IL-21, and IL-22 [24, 25] (Table 2). IL-6 functions in both innate and adaptive immunity. It is secreted in response to microbes, IL-1, and TNF- α , and its signaling is mediated by Jak1 and Tyk2

Table 2 Source and functions of key cytokines in HIES [6, 7, 22]

Cytokine	Known functions
IL-6	Produced by: mononuclear phagocytes, T and B cells, fibroblasts, hepatocytes, endothelial cells, keratinocytes, bone marrow cells Effects: Proinflammatory, activates neutrophils, activates T and B cells, potent stimulator of hepatic acute phase protein production, induces pulmonary fibrosis by fibroblast proliferation and collagen deposition Anti-inflammatory: inhibits further production of IL-1 and TNF- α
IL-10	Produced by primarily by Treg, monocytes, and B cells Effects: Proinflammatory: stimulates B cells and immunoglobulin production, particularly IgG4 Anti-inflammatory; decreases production of IFN- γ , IL-1B, 2, 4, 5, 6, 8, 12, TNF- α ; inhibits eosinophil survival and IgE production; downregulates TNF- α synthesis
IL-17	Produced by Th17 cells and eosinophils Effects: activates macrophages, fibroblasts, stromal cells; induces IL-6, IL-8, IL-11, and G-CSF expression. Enhances macrophage production of nitric oxide and prostaglandin E2; role in airway remodeling
IL-21	Produced by T cells Effects: activates NK and CD8 cells and promotes both T and B cell proliferation. Acts with IL-4 cells to induce B cell class switching
IL-22	Produced by T cells, Th17 cells, activated NK cells Effects: upregulates epithelial innate molecules leading to epithelial defense; expression is induced by TLR 9; induces acute phase protein production
TNF- α	Produced by: macrophages neutrophils, NK cells, endothelial cells, mast cells Effects: cytotoxic antitumor immunity, induces ICAM, VCAM, and selectin expression to induce neutrophil adhesion to the endothelium and facilitate migration to the periphery; potent neutrophil activator; induces vascular leakage, negative ionotropic effects, inhibits eosinophil apoptosis
IFN- γ	Produced by T cells and NK cells; some macrophages Effects: key cytokine in cell-mediated immunity; increases MHC I and II expression. Induces TNF- α production, stimulates macrophage response to microbes via adherence, nitric oxide production, phagocytosis, oxidative burst, etc. Also stimulates effects of NK cells and neutrophils. Inhibits IgE production
IL-12	Produced by monocytes, macrophages; also from B cells, dendritic cells, Langerhans cells, PMNs and mast cells Effects: enhances growth and activity of NK cells, induces IFN- γ production, induces T cell proliferation

leading to *STAT3* activation. IL-6 induces acute phase proteins by hepatocytes, neutrophil production in cooperation with colony-stimulating growth factors, stimulation of differentiated B cell growth, stimulation of proinflammatory cytokine production (particularly IL-17), and inhibition of the action and production of regulatory T cells [24]. MCP-1 (also known as CCL2) induces chemotaxis and cytokine expression by a broad range of cells and is normally upregulated by IL-6. However, the increase in MCP-1 after IL-6 stimulation in HIES patients is blunted [5].

Due to impaired IL-6 and IL-23 function via *STAT3*, the transcription factor ROR- γ is diminished, further impairing IL-17 expression and Th17 differentiation [26–29]. Th17 cells produce IL-17, IL-21, and IL-22, and are thought to be important in defense against fungi and extracellular bacteria, most likely due to their role in neutrophil recruitment, activation, and antimicrobial peptide expression [30–33]. SH2 or DNA-binding region *STAT3* mutations introduced into normal cells diminished ROR- γ expression. The specific role of IL-17 deficiency in HIES is still being determined but candida infection occurs in IL-17 deficient mice [32]. In addition, IL-17 neutralization in mice leads to eosinophilia [34] and IL-21 haploinsufficient mice have increased IgE [35]. Conversely, recent data in humans suggest that IL-21 acts synergistically with IL-4 to increase IgE secretion [36]. IL-22, via *STAT3*, stimulates skin beta-defensin production, which may explain some of the susceptibility to epithelial infection [37].

The frequent development of pneumatocoles following pneumonias, despite adequate therapy for sensitive pathogens, has long suggested abnormal regulation of the inflammatory response. Transcriptional array studies and cytokine production studies both show upregulation of proinflammatory cytokines [5, 38]. HIES patient cells showed increased TNF α production after stimulation with LPS, LPS with IFN- γ , *S. aureus*, or heat-killed *Listeria*; increased IL-12 production was found after stimulation with LPS or LPS with IFN- γ [5]. Although IFN- γ typically prolongs neutrophil survival, this was not seen in HIES patients, suggesting that *STAT3* may regulate other aspects of neutrophil apoptosis as well. Myeloid-specific *STAT3*-deficient mouse models have increased susceptibility to endotoxin-induced shock and increased expression of IFN- γ and IL-1 [39], some of which may be due in part to impaired IL-10 signaling. IL-10 is produced mainly by macrophages and regulatory T cells and signals through Jak1, Tyk2, and *STAT3* [25]. IL-10 is an anti-inflammatory cytokine that has negative feedback regulation of macrophages, which express costimulators that enhance T cell activation and secrete cytokines such as IL-12 and IL-23 to enhance cell-mediated immunity. Therefore, impaired IL-10 signaling may be associated with increased proinflammatory cytokines and may contribute to increased IgE and

eosinophilia due to the lack of normal IL-4 suppression [40].

Non-immunologic phenotypes of HIES

While the homozygous mouse *STAT3* knock out was embryonic lethal due to defects in development of visceral endoderm [41], tissue-specific *STAT3* deletions have shown poor wound healing, defective cardiomyocyte function, eosinophilia, osteopenia, impaired b-defensin production, and pulmonary cyst formation. Some of these non-immunologic findings in mouse models correlate with clinical findings in HIES patients.

Lung

Pulmonary epithelium-specific *STAT3* deficiency shows excessive inflammation and airspace enlargement with poor repression of inflammatory response to intrapulmonary delivered LPS [42]. This may correlate with post-infectious pneumatoceles seen in HIES lung.

Bone

Myeloid-specific *STAT3*-deficient mice have increased osteoclast numbers and activity leading to osteoporosis [43]. Similarly, there is an increase in formation of osteoclasts and higher bone resorption activity of osteoclasts from HIES patients [44]. This may be due to both decreased IL-10 activity and increased TNF α levels. IL-10 normally acts to inhibit osteoclast activity, while TNF α increases osteoclast development and activity [45]. TNF α also has an inhibitory effect on osteoblasts, which may compound the osteopenia. However, in in vitro models of osteoclastogenesis, *STAT3* has both proliferative and inhibitory effects on osteoclasts [46]. The underlying mechanism of the skeletal features of HIES and their optimum treatment are unclear.

Brain

Astrocyte-specific *STAT3* deficiency in mice led to increased inflammation, demyelination, and astrogliosis after neurologic injury, possibly from the disruption of IL-6 signaling in astrocyte differentiation [47]. Demyelination in the mouse model may correlate with the cerebral T2-weighted hyperintensities seen on brain MRI in HIES [17].

Heart

Cardiac myocyte-specific *STAT3* deficiency in the mouse is associated with decreased left ventricular capillary density and propensity to develop heart failure and increased infarct

size after ischemic insult [48]. These mice also demonstrated impaired angiogenesis due to decreased endothelial but increased fibroblast proliferation. Additionally, after stimulation with LPS, increased TNF α levels with subsequent cardiac inflammation and dysfunction were demonstrated [49]. Myocardial dysfunction has not been a reported feature of HIES but as survival increases these findings may appear. Coronary artery tortuosity and aneurysm formation with paucity of atherosclerosis have been reported [15] but the mechanism of the aneurysm formation remains unknown. Some mouse models of atherosclerosis are associated with increased *STAT3* expression [50] suggesting that decreased expression of *STAT3* may be associated with less atherosclerosis. This supposition is supported by our preliminary evidence (Freeman AF and Gharib A, unpublished data).

Skin

Mouse keratinocytes lacking *STAT3* were associated with normal initial hair growth but aberrant hair follicles in subsequent growth cycles, leading to epidermal hyperplasia and keratosis. After skin biopsy these mice demonstrated poor wound healing [51]. Although poor wound healing is not typically described in HIES, these findings may relate to the characteristic porous facial skin [3, 4], the oral mucosal abnormalities [13], and eczema that develop in HIES over time.

Autosomal recessive hyper IgE syndrome

Autosomal recessive diseases with elevated IgE that have been grouped with HIES are considerably more rare than the autosomal dominant *STAT3*-deficient form of HIES. They are clinically distinct, more severe, and may be associated with autoimmunity and vasculitis [52]. Along with severe atopic dermatitis and recurrent skin infections, these patients have serious cutaneous viral infections with *Molluscum contagiosum*, Herpes simplex virus, and Varicella zoster. Although pneumonias may occur, these individuals do not form pneumatoceles and have no connective tissue abnormalities. Mortality is high in childhood, commonly due to bacterial sepsis or CNS vasculitis. Specific mutations have not been identified in these patients. However, a single case of homozygous mutation leading to a premature stop in Tyk2 was found [53]. Tyk2 is a key signal transduction molecule upstream of *STAT3* and therefore critical for the production of IL-6, IL-10, IL-12, IL-23, and IFN- α , many of the same cytokines involved with *STAT3*. This Tyk2 deficient patient was somewhat phenotypically distinct from the other autosomal recessive HIES patients, having non-*Typhi*

Salmonella infections and BCG lymphadenitis. Neither *Tyk2* nor *STAT3* mutations have been found in other individuals with AR-HIES.

Conclusion

HIES remained a pathogenetic enigma for decades after its initial clinical description. The identification of specific mutations in the JAK-STAT signal transduction pathway in these patients has primed us to dissect the etiology and pathophysiology of these far-flung disorders, ranging from eczema to aneurysms. Identification of these mutations will improve the timing and precision of diagnosis, and may permit earlier definitive identification. Further understanding of the pathogenesis of the complex features of HIES should allow for more effective and targeted treatment. Since many of the cardinal features of HIES, such as staphylococcal infection, scoliosis, and osteoporosis are common in the general population, it is hoped that understanding how *STAT3* defects cause these problems will help guide us toward more rational and better treatments in the future.

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