

Genetic Origins of Hyper-IgE Syndrome

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Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency characterized by high serum IgE, chronic eczematoid dermatitis, and recurrent extracellular bacterial infections. Two types of HIES have been reported: type 1 and type 2. Type 1 HIES displays abnormalities in multiple systems, including the skeletal, dental, and immune systems, whereas type 2 shows abnormalities confined to the immune system. We recently identified hypomorphic mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene in type 1 HIES and a null mutation in the tyrosine kinase 2 (*Tyk2*) gene, accompanied by susceptibility to intracellular bacteria in type 2 HIES. Analyses of cytokine responses in both types of HIES revealed that severe defects in the signal transduction for multiple cytokines, including interleukin-6 and interleukin-23, are leading to impaired T-helper type 17 function. These findings suggest that HIES is caused by the defects in multiple cytokine signals and that the susceptibility to various infections in HIES is associated with the T-helper type 17 defect.

Introduction

Clinical features and a classification of the HIES

Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disorder characterized by high levels of serum IgE, atopic dermatitis, and recurrent bacterial infections [1,2]. The IgE levels in the serum are often 10 to 1000 times higher than those of normal individuals. The atopic dermatitis-like skin lesion usually starts in the neonatal period, and the extracellular bacterial infections generally commence in infancy or early childhood and mainly involve the skin and airway. The most common bacteria involved in the infections are *Staphylococcus aureus*, although *Streptococcus pneumoniae*, *Haemophilus influenza*, and enteric gram-negative bacteria are occasionally isolated in some infectious episodes of the patients.

Most cases of HIES are sporadic, but some familial cases have been reported with autosomal dominant (AD) [3] or autosomal recessive (AR) mode of inheritance. Skeletal and dental abnormalities, such as characteristic facial appearance, hyperextensibility of joints, scoliosis, fracture with minor trauma, and retained primary teeth, are observed in sporadic and familial cases with the AD form. The AR form is characterized by severe recurrent viral infections, extreme eosinophilia, and neurologic complications. From clinical and etiologic points of view, we have proposed a new classification of HIES divided into two groups—type 1 and type 2—irrespective of modes of inheritance.

Type 1 HIES

This group of HIES represents the most common and typical form and includes sporadic and familial AD types [3]. In addition to the recurrent skin and pulmonary infections, atopic dermatitis, and elevated serum IgE, type 1 HIES patients present with skeletal, dental, and connective tissue manifestations (Table 1). By age 16 years, all patients show distinctive facial appearance: coarse texture of facial skin, asymmetric facial appearance, prominent forehead, deep-set eyes, broad nasal bridge, and bulky nasal tip. In this type of HIES, pneumonia is frequently followed by the formation of pulmonary cysts (pneumatocoles), most likely due to the impaired remodeling capability of the lung tissue. Pulmonary cysts are frequently complicated by the superinfection of *Aspergillus* spp and multidrug-resistant *Pseudomonas aeruginosa*, which is a serious problem in the morbidity and mortality of HIES patients [4].

Type 2 HIES

This second group of HIES was reported relatively recently, as six consanguineous families from Turkey and Mexico were found to carry the AR form of HIES [5]. The patients in these families showed no apparent abnormalities in their skeletal and dental systems but suffered from recurrent and severe infections with *S. aureus*, *S. pneumoniae*, or *H. influenzae*, as observed in type 1 HIES. Most of the type 2 HIES patients also suffered from severe viral infections, such as chronic refractory molluscum contagiosum and herpes simplex virus infections, which were not observed in type 1 HIES. Furthermore, unlike in the type 1 HIES patients, no pneumatocoles were formed in any of the type 2 HIES patients, even though the incidence of pneumonia was equivalent in the two types. Seven of 13 patients with type 2 HIES had neurologic complications,

Table 1. A new classification of hyper-IgE syndrome

Type	Inheritance	Distinguished clinical findings
Type 1 (multisystem)	Sporadic (most cases); familial with AD inheritance (rare)	Skeletal and dental abnormalities (characteristic face, fracture with minor trauma, retained primary teeth, scoliosis, hyperextensibility); parenchymal lung abnormality
Type 2 (nonskeletal)	Familial with AR inheritance	Severe viral infections (herpes simplex, molluscum contagiosum); possible CNS involvement

AD—autosomal dominant; AR—autosomal recessive; CNS—central nervous system.

and four of them died as a result. The neurologic complications may be primary to the type 2 HIES or secondary to latent infections to the central nervous system because of the immunodeficiency.

Janus Kinases and Signal Transducers and Activators of Transcription in Cytokine Signaling

Cytokines regulate cell development, homeostasis, and differentiation. Most cytokines transduce signals using receptors devoid of intrinsic kinase activity. Janus kinases (Jaks) constitutively associated with the cytoplasmic domain of cytokine receptors phosphorylate receptor subunits upon ligand binding, which then recruit and phosphorylate signal transducers and activators of transcription (STATs) to the receptor (Fig. 1). Once phosphorylated, STATs dimerize via their Src homology 2 (SH2) domains and translocate to the nucleus, where they activate a series of STAT-regulated genes.

Four mammalian Jak proteins—Jak1, Jak2, Jak3, and tyrosine kinase 2 (Tyk2)—have been described [6–8]. The functional importance of the Jaks was demonstrated by studies in cell lines defective in cytokine signaling and subsequently confirmed by the establishment of Jak-deficient mice [9–14]. Jak1^{-/-} mice die perinatally and exhibit profound defects in lymphoid development related to the failure of γ c-using cytokine receptor signaling. Analyses of cells from Jak1^{-/-} mice demonstrated that Jak1 was essential for signaling by type 1 and type 2 interferon (IFN), a finding that was in agreement with prior studies using human mutant cell lines. Jak2^{-/-} mice show embryonic lethality due to failure of erythropoiesis, whereas Jak3^{-/-} mice suffer from severe combined immunodeficiency in accord with the observation in human Jak3 deficiency [15,16]. These findings clearly demonstrated the nonredundant roles of Jak1, Jak2, and Jak3 in signaling through the corresponding cytokine receptors.

Tyk2 was the first member of the Jak kinase family to be isolated and was originally described as essential to the type 1 IFN signaling in a human fibroblast cell line [17,18]. However, the establishment of Tyk2-deficient mice revealed that Tyk2 was not absolutely essential for responses to type 1 IFN in mice [19,20]. Tyk2^{-/-} mice displayed a lack of responsiveness to a small amount of IFN- α , but a high

concentration of IFN- α could fully transduce signals even in the absence of Tyk2. Although Tyk2 is a component of several other cytokine-signaling pathways, including those of interleukin-6 (IL-6), IL-10, and IL-12 [6,21,22], in the Tyk2^{-/-} mice, the IL-6-mediated signals are essentially normal, and the IL-12 signal is partially impaired. Thus, the function of Tyk2 in mice appears to be compensated for in vivo, partly by other kinase(s), most likely other Jaks. It remains to be determined whether the discrepancy in the stringency of Tyk2 requirement in the cytokine signaling between the human cell lines and the mutant mice can be attributed to the difference between established cell lines and primary cells or the species difference, as observed in several primary immunodeficiencies, such as the Bruton tyrosine kinase (Btk), B-cell linker protein (BLNK), or λ 5 deficiency [23–25].

STAT3 was originally identified as a transcription factor that binds to the promoters of various acute-phase protein genes [26–29]. It plays a critical role in the signal transduction of many cytokines, including IL-6, IL-10, IL-22, IL-23, and IL-27 [30–32]. A null mutation of the STAT3 gene in transgenic mice demonstrated that STAT3 is essential to embryonic survival near the time of implantation (E6.5–E7.5) [33]. Tissue-specific deletion of STAT3 was not lethal in various organs, including the skin, mammary glands, liver, thymic epithelium, respiratory epithelium, neurons, lymphocytes, and macrophages [34]; this deletion demonstrated the critical role of STAT3 in cell migration, survival, proliferation, apoptosis, and inflammation in each tissue. Of interest, STAT3 is frequently activated in human cancers, occurring in more than half of breast and lung cancers, hepatocellular carcinomas, and multiple myelomas and more than 95% of head and neck cancers. Moreover, in cultured tumor cells from more than a dozen different cancers, interruption of the persistent STAT3 activity by dominant negative proteins or antisense oligonucleotides leads to apoptosis in cancer cells. Activated STAT3 plays a crucial role in the survival and proliferation of cancer cells [35].

Etiology of HIES

HIES, also called Job's syndrome, was first described in 1966 by Davis et al. [36] in two patients who had severe dermatitis and recurrent staphylococcal skin infections that

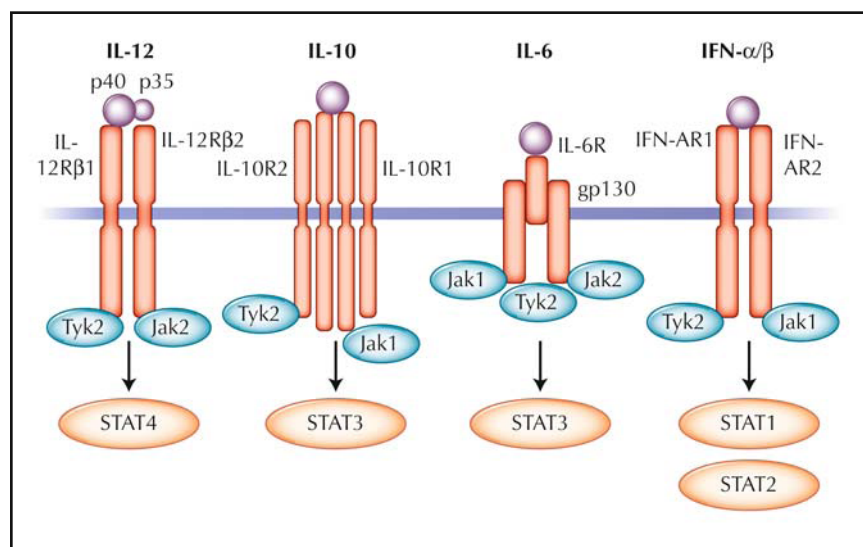


Figure 1. Receptors, Jaks, and STATs in cytokine signaling. IFN—interferon; IL—interleukin; Jak—Janus kinase; STAT—signal transducer and activator of transcription; Tyk—tyrosine kinase.

were distinguished by the lack of inflammation features, which they coined *cold abscesses*. Buckley et al. [37] further characterized the syndrome, noting similar impaired inflammation in patients with highly elevated serum IgE levels. The origin and molecular pathology of HIES remain an enigma more than 40 years after the original report. Recent studies have focused on the T-helper type 1 cell (Th1)/Th2 cytokine imbalance. Although some studies suggested that the presence of decreased Th1 cytokine production and skewing toward Th2 cells [38–40], the results were inconsistent and did not provide significant clues to identify molecular origins of HIES. In patients with defects in the IL-12 signaling, none of the features or infections of HIES are seen, suggesting that the simple reduction of IFN- γ in response to IL-12 is unlikely to cause HIES [41].

Tyk2 deficiency as a genetic origin of a subpopulation of type 2 HIES

The first genetic origin of HIES was a null mutation of Tyk2 involved in the signaling of many cytokines [6,42••]. The patient had a homozygous Tyk2 mutation that resulted in a premature stop codon (hence the absence of Tyk2 protein). The patient's parents were consanguineous, and both were heterozygous for the mutation, establishing the AR inheritance of the Tyk2 deficiency in the patient. The Tyk2-deficient patient displayed typical phenotypes of type 2 HIES, including elevated serum IgE, atopic dermatitis, staphylococcal infections in the skin and lung, and viral infections in the skin and mucosa (but no skeletal and dental abnormalities). The patient also displayed susceptibility to intracellular bacteria.

Blood cells from the patient showed severe defects in responses to multiple cytokines, including type 1 IFN, IL-6, IL-10, IL-12, and IL-23 (Fig. 1). The cytokine signals were successfully restored by transducing the intact *Tyk2* gene. Thus, the Tyk2 deficiency is likely to account for the patient's clinical manifestations. The patient's susceptibility to viral infections could be explained by the defects in

type 1 IFN signaling due to the Tyk2 deficiency. IFN- α -induced tyrosine phosphorylation of Jak1, STAT1, STAT2, and STAT3 was completely abrogated in the human Tyk2-deficient cells, in contrast to the observation in the Tyk2-deficient mice [19,20]. Furthermore, no inhibition in the replication of herpes simplex virus was observed in the patient's cells when the cells were pretreated with IFN- α . Thus, unlike in mice, Tyk2 plays a nonredundant role in type 1 IFN signaling in humans. One characteristic feature of the human Tyk2 deficiency was the susceptibility to infections with intracellular bacteria such as mycobacteria and salmonella. The absence of Tyk2 resulted in the defects of IL-12 and type 1 IFN signaling, which led to impaired Th1 differentiation and IFN- γ production. This defect likely accounts for the patient's susceptibility to intracellular bacterial infections as reported in other disorders with the defects in the IL-12 and IFN- γ signaling circuit [43]. When the patient's naïve CD4 T cells were cultured in vitro, accelerated Th2 differentiation was observed in addition to the impaired Th1 differentiation, reflecting the patient's Th2-dominant phenotypes, such as atopic dermatitis, asthma, and elevated serum IgE levels. As IL-10 plays a critical role in the peripheral T-cell tolerance to allergens, it would be reasonable to assume that allergic symptoms in the Tyk2 deficiency were associated at least partially with the defective IL-10 signaling.

Hypomorphic mutations in STAT3 cause type 1 HIES

The identification of the Tyk2 deficiency in the type 2 HIES patient suggested to us that a similar defect in cytokine signaling may be observed in type 1 HIES. Therefore, we examined the responses to IL-6, IL-10, IL-12, and IFN- α of peripheral blood cells from the patients presenting with typical clinical characteristics of type 1 HIES. Both IL-6 and IL-10 signaling pathways were defective in type 1 HIES, as in the Tyk2 deficiency. In contrast, neither IL-12 nor IFN- α signaling was impaired in the type 1 HIES patients [44••].

In a survey of candidate molecules involved in IL-6 and IL-10 signaling, we identified heterozygous mutations in *STAT3* in 8 of 15 type 1 HIES patients: a single amino acid deletion ($\Delta V463$) or missense mutations in the DNA-binding domain [44••]. The DNA-binding domain of *STAT3* is highly conserved among different species in its amino acid sequence, and the alterations were not found in 1000 unrelated healthy individuals who were analyzed. *STAT3* is located on human chromosome 17q21 but not 4q, which was reported to contain a disease locus for familial AD-HIES [45]. None of the eight HIES patients in our study had a known family history of HIES, and no mutation was detected in the *STAT3* cDNAs from all the parents and seven siblings of the patients. Therefore, the mutations are likely to have occurred de novo in the HIES patients.

A recent study confirmed our findings that *STAT3* is a major causing gene for type 1 HIES. Two groups identified heterozygous mutations in the *STAT3* gene in most of the patients with type 1 HIES, including the original patients reported by Holland et al. [46] and Renner et al. [47]. The mutations were located in the DNA-binding domain of *STAT3* in the first eight patients, which extended to the SH2 domain of *STAT3*. Although clinical characteristics are identical among the patients with the mutations in the DNA-binding domain and those in the SH2 domain, it is not clear whether or how the mutation in the SH2 domain functions as dominant negative. By analogy with mutations in *STAT1*, the mutations in *STAT3* may be present in the transactivation domain [48].

STAT3 plays important roles in the differentiation of osteoblasts and osteoclasts in vitro, and mice deficient for *STAT3* in osteoblasts show an osteoporotic phenotype [49]. When osteoclasts were generated from peripheral blood monocytes in culture with macrophage colony-stimulating factor and receptor activator of nuclear factor- κ B ligand, those from the HIES patients with the *STAT3* mutations showed higher bone-resorption activity compared with those from controls. This may reflect the skeletal and dental abnormalities observed in HIES patients. Another remarkable clinical feature of HIES is that patients are often afebrile and feel well [2] despite serious pneumonia or dermal pathology (cold abscess) [36]. Moreover, acute-phase responses such as an increase in serum C-reactive protein during infections were diminished in our patients. *STAT3* was originally identified as a protein binding to the IL-6-responsive element in the genes encoding hepatic acute-phase proteins [26], and the liver-specific inactivation of *STAT3* led to an impaired acute-phase response in mice. Thus, the apparent lack of classical inflammatory responses in HIES patients could be attributed to defective IL-6 signaling.

STAT3 plays a critical role in Th17 development in mice [50], and IL-17 produced by Th17 cells is protective in the host defense against extracellular bacteria [51–53]. IL-22 stimulates cells in the skin and respiratory systems to produce β -defensins through *STAT3* activation [54,55].

Thus, the susceptibility to extracellular bacterial infection could be attributed, at least in part, to the defects in Th17 development and IL-22 signaling. Defective Th17 development and function in HIES patients with mutations in *STAT3* was recently demonstrated [56]. Future studies should clarify how defective Th17 cells specifically cause the susceptibility to staphylococcal infections in the skin and the lungs.

Treatment

Treatment regimens that are most effective for HIES patients are preventive oral antibiotics. Antistaphylococcal penicillins were among the most widely used treatments. However, as more cases with multidrug-resistant *S. aureus* evolve, the selection of antibiotics needs to be reconsidered. Trimethoprim-sulfamethoxazole is safe and effective and has anti-methicillin-resistant *S. aureus* properties. Long-term, preventive trimethoprim-sulfamethoxazole with periodic monitoring associated with culture-directed antibiotics and antifungals is recommended for mainstay treatment of HIES patients. As described previously, it is important that physicians be careful about seemingly mild symptoms in HIES patients, which frequently require extensive assessments and aggressive interventions.

The identification of *STAT3* as a major causing gene for type 1 HIES enables us to definitively diagnose patients with HIES very early. The key feature for early diagnosis is newborn rash, which is frequently associated with the susceptibility to staphylococcal infections and high serum IgE. Earlier definitive diagnosis allows the start of oral antibiotics earlier, which should prevent the pneumatocele formation. Prevention is likely to improve the morbidity and mortality of patients with HIES.

Conclusions

Type 1 HIES has three unique features: 1) susceptibility to *S. aureus* infection in the skin and the lungs; 2) defective formation of a normal “warm” abscess, which is likely to result from inefficient inflammation; and 3) skeletal and dental abnormalities. None of the other primary immunodeficiencies demonstrated the identical manifestations with HIES. In addition, although a few other primary immunodeficiencies show extremely high serum IgE and atopic dermatitis-like skin lesions, these intriguing clinical manifestations have attracted the attention of many physicians and scientists. The identification of the hypomorphic mutations in the *STAT3* gene in most of the patients with HIES revealed that the abnormalities in the signal transduction of multiple cytokines are likely to be responsible for the pathogenesis of HIES, although the exact molecular mechanism of this syndrome is still unclear. Future studies should clarify this syndrome’s molecular pathology, which may provide new insights into more common diseases, including autoimmunity, osteoporosis, or allergy.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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