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Current Opinion in
Immunology

Hyper-IgE syndrome

Yoshiyuki Minegishi

Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency characterized by atopic dermatitis associated with extremely high serum IgE levels and susceptibility to infections with extracellular bacteria. Nonimmunological abnormalities, including a distinctive facial appearance, fracture following minor trauma, scoliosis, hyperextensive joints, and the retention of deciduous teeth are also observed in most patients. Recent studies have demonstrated that *dominant-negative* mutations in the signal transducer and activator of transcription 3 (STAT3) gene result in the classical multisystem form of HIES, whereas a null mutation in the tyrosine kinase 2 (TYK2) gene causes an autosomal recessive HIES associated with viral and mycobacterial infections. In both patients, signal transduction for multiple cytokines, including IL-6 and IL-23, was defective, resulting in impaired T_H17 function. These findings suggest that the defect in cytokine signaling constitutes the molecular basis for the immunological and nonimmunological abnormalities observed in HIES.

Address

Department of Immune Regulation, Graduate School, Tokyo Medical and Dental University, 1-5-45 Bunkyo-ku, Yushima, Tokyo 113-8519, Japan

Corresponding author: Minegishi, Yoshiyuki
(yminegishi.mbch@tmd.ac.jp)

Current Opinion in Immunology 2009, 21:1–6

This review comes from a themed issue on
Primary Deficiencies
Edited by Jean-Laurent Casanova and Luigi Notarangelo

0952-7915/\$ – see front matter
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DOI 10.1016/j.coi.2009.07.013

Introduction

Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disorder (PID) characterized by recurrent staphylococcal infections in the skin and lung, chronic eczema, and markedly high serum IgE concentrations [1–5]. Davis and Wedgwood first described this disease in 1966, in two girls suffering from recurrent ‘cold’ staphylococcal abscesses, pneumonia, and neonatal-onset eczematoid rash [6]. As this original report predated the identification of IgE [7], a high serum concentration of IgE level was not recognized in these patients. This syndrome was characterized further by Buckley *et al.*

[8], who found that recurrent staphylococcal abscesses and chronic eczema were associated with exceptionally high serum concentrations of IgE. They also showed that serum concentrations of the other immunoglobulins (IgG, IgA, IgM, and IgD) and IgG subclasses were normal in the patients. The multisystem nature of HIES was established later, when manifestations of the disease were shown to extend beyond immune system abnormalities, to encompass skeletal and connective tissue abnormalities, such as scoliosis, osteoporosis, fracture following minor trauma, hyperextensive joints, and the retention of deciduous teeth [9]. In 2004, a novel form of HIES was identified in consanguineous families, suggesting the presence of autosomal recessive (AR) forms of HIES [10]. In 2006, a tyrosine kinase 2 (TYK2) deficiency was identified in an AR-HIES patient associated with susceptibility to intracellular bacterial and viral infections [11]. Finally, in 2007, *dominant-negative* mutations in the signal transducer and activator of transcription 3 (STAT3) gene were identified as a major molecular etiology of classical HIES [12,13]. In this review, I will outline the clinical signs, molecular origins, and pathogenesis of HIES. I will also discuss several unanswered questions concerning the pathogenesis of HIES and potential directions for future research.

Clinical manifestations

Almost all patients with HIES suffer from recurrent staphylococcal infections, beginning in infancy and predominantly involving the skin and lungs [1–5,14]. This situation contrasts starkly with that in patients with chronic granulomatous disease (CGD), in which recurrent staphylococcal infections occur in a wide variety of organs, including the lung, lymph nodes, skin, liver, bone, gastrointestinal tract, kidney, and brain [15]. *Staphylococcus aureus* is the bacterium most frequently isolated from HIES patients, but *Streptococcus pneumoniae*, *Haemophilus influenzae*, and enteric Gram-negative bacteria are occasionally isolated from HIES patients, during episodes of infection. Fungal infections, including mucocutaneous candidiasis and pulmonary aspergillosis, are also common in HIES. Eczema usually begins during the neonatal period, before the onset of atopic dermatitis. Patients with HIES suffer from atopic dermatitis associated with extremely high serum IgE levels and eosinophilia, but are usually free from other allergic manifestations, such as allergic rhinitis, asthma, urticaria, and anaphylaxis.

In this review, HIES is classified into two categories, type 1 and type 2, regardless of its mode of inheritance. Patients with type 1 HIES have abnormalities in multiple systems of the body, including the skeletal and dental systems,

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Table 1

A classification of HIES

HIES type	Inheritance	Discriminant clinical findings
Type 1	Sporadic (more than 90% of cases) Familial with autosomal dominant inheritance (rare)	Skeletal and connective tissue abnormalities (characteristic facial appearance, fracture following minor trauma, retention of deciduous teeth, scoliosis, hyperextensibility), pneumatocele
Type 2	Familial with autosomal recessive inheritance	Viral infections (herpes simplex virus, molluscum contagiosum) Central nervous system involvement Some mycobacterial infections Absence of pulmonary cysts Absence of skeletal abnormalities

whereas patients with type 2 HIES have abnormalities confined to the immune system (Table 1). Type 1 HIES is the most common form, and was the type presented by the cases reported by Davis and Buckley [6,8]. In this type of HIES, pneumonia is frequently followed by the formation of pneumatocele or pulmonary cysts, frequently complicated by infections with *Aspergillus* and multidrug-resistant *Pseudomonas aeruginosa* [16[•]]. Patients with type 2 HIES have no skeletal abnormalities, but suffer from recurrent viral infections, such as molluscum contagiosum and herpes simplex virus (HSV) infections [10]. No pneumatocele was found in patients with type 2 HIES. Most type 2 HIES patients have been found to have mild defects in signal transduction downstream from the T-cell receptor (TCR) complex.

Etiology of HIES

A null mutation in TYK2 results in a variant form of type 2 HIES

TYK2 deficiency was identified as a molecular cause of type 2 HIES based on the finding that a type 2 HIES patient was susceptible to intracellular bacterial infection and had a defect in signal transduction for IL-12 and IFN α [11]. Unlike other patients with type 2 HIES, this TYK2-deficient patient displayed intact TCR signaling. TYK2 is one of the founding members of the Janus kinase family (Jaks), transducing a signal downstream from a number of cytokines [17,16[•],18–21]. The patient had a homozygous four-base pair deletion in the coding region of the *TYK2* gene, resulting in a premature stop codon and the absence of TYK2 protein. The parents of the patient were consanguineous and heterozygous for the 4-bp deletion. Both parents displayed normal immune responses, consistent with the AR inheritance of TYK2 deficiency. This disorder was named AR-HIES with mycobacterial and viral infections by the PID classification committee of the International Union of Immunological Societies (IUIS) [22].

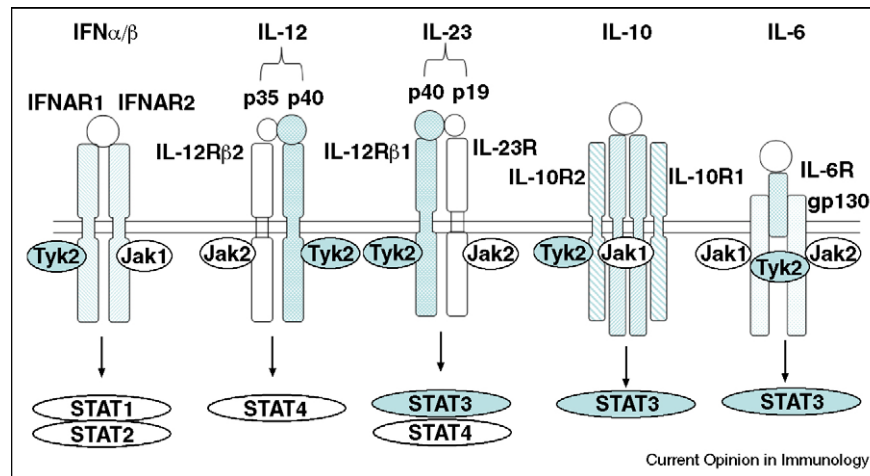
Cells from the patient displayed severe defects in response to a number of cytokines, including type 1 IFN, IL-12, IL-23, IL-10, and IL-6 (Figure 1) [11]. The signal transduction initiated by these cytokines was restored by transduction

with the wild-type *TYK2 in vitro*, suggesting that TYK2 deficiency was responsible for the clinical signs observed in the patients. The susceptibility of the patient to viral infections probably resulted from the defects in type 1 IFN signaling. IFN α -induced tyrosine phosphorylation of JAK1, STAT1, and STAT2 was abolished. Furthermore, no inhibition of HSV replication was observed after treatment of the patient's cells with a large dose of IFN $\alpha in vitro$. Thus, TYK2 plays a nonredundant role in type 1 IFN signaling in humans, but not in mice [23,24]. Patients with *STAT1* mutations impairing both IFN γ and IFN α/β signaling suffered from both mycobacterial disease and disseminated HSV-1 infection [25]. These data indicate that human type 1 IFN plays a crucial role in the immunological control of HSV. The absence of TYK2 resulted in defective IL-12 signaling, leading to impaired T_H1 differentiation and IFN γ production and susceptibility to intracellular bacterial infections. This is consistent with the observation that patients with IL-12B and IL-12RB1 deficiencies are susceptible to intracellular bacterial infections [26]. Impaired Th1 differentiation and accelerated Th2 differentiation probably resulted in atopic dermatitis, asthma, and high serum IgE levels in the TYK2-deficient patient.

A dominant-negative mutation in STAT3 causes type 1 HIES

The identification of TYK2 deficiency in a type 2 HIES patient led us to investigate the responses to multiple cytokines in type 1 HIES patients. Signaling was found to be defective for IL-6 and IL-10, whereas signaling was intact for IL-12 and IFN α . In a survey of candidate genes, we identified heterozygous mutations affecting the DNA-binding domain of STAT3 in patients [12^{••}]. None of the HIES patients had a family history of HIES, and no mutation was detected in the parents. These mutations therefore probably occurred *de novo* in the patients. *STAT3* mutations were subsequently identified in most of the patients with type 1 HIES, including the patients described in the first report of HIES [13,27[•],28,29]. These mutations were located in the DNA-binding domain in our eight patients, and were subsequently shown to affect the Src-homology 2 (SH2) domain, the linker domain, and the transactivation domain of STAT3 [30].

Figure 1



Cytokine receptors and the associated intracellular Jaks (Jak1, Jak2, and Tyk2) and STATs.

STAT3 is a transcription factor that binds to the STAT3-responsive elements in the promoters of various genes, including those encoding acute-phase proteins [19,20]. STAT3 plays a critical role in responses to many cytokines and growth factors, including γ c cytokines (IL-2, IL-7, IL-9, IL-15, and IL-21), IL-6/gp130 cytokines (IL-6, IL-11, IL-27, IL-31, CNTF, CT-1, oncostatin M, and leukemia inhibitory factor), type 1 and type 2 IFNs (IFN α , IFN β , and IFN γ), IL-10 family cytokines (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29), receptor tyrosine kinases (EGF, FGF, Flt3 ligand, GH, IGF1, M-CSF, and PDGF), as well as IL-5, IL-12, IL-23, G-CSF, leptin, and PAF. A study of a null mutation in the STAT3 gene in mice demonstrated that STAT3 was essential for the survival of the embryo around the time of implantation [31]. Studies of mice with tissue-specific deletions of *STAT3* have shown STAT3 to play a crucial role in cell proliferation, survival, migration, apoptosis and inflammation in various tissues, organs and cells, including skin, respiratory epithelium, thymic epithelium, liver, mammary glands, neurons, lymphocytes, and macrophages [32]. Many of the clinical signs of type 1 HIES patients therefore probably reflect defects of the diverse functions of STAT3 *in vivo*.

Pathogenesis

Our knowledge of the pathogenesis of HIES in patients with *STAT3* mutations remains limited, despite the discovery of the molecular etiology of HIES. Several major questions remain unanswered: first, What is the molecular mechanism underlying atopic dermatitis and high serum IgE levels in these patients? second, What is the molecular mechanism underlying the observed skeletal abnormalities?

Staphylococcal infection of the skin and lung

T_H17 cells are a newly identified subset of helper T-cells associated with the exacerbation of various autoimmune

disorders, including inflammatory bowel disease, multiple sclerosis, psoriasis, and rheumatoid arthritis [33–41]. T_H17 cells produce T_H17 cytokines, including IL-17 (IL-17A), IL-17F, and IL-22. Their functions in humans remain unclear, but there is evidence to suggest that T_H17 cells play a crucial role in the recruitment of neutrophils and production of the antimicrobial peptides β -defensin 2 (BD2) and BD3 by epithelial and endothelial cells.

Recent studies have demonstrated defects in the differentiation of T_H17 cells in patients with HIES [27^{*},29,42^{*},43^{*}]. The occurrence of staphylococcal infections in HIES patients suggests that T_H17 cells play a crucial role in protecting against *S. aureus*, not only in mice but also in humans. However, these infections are usually confined to the skin and lungs. We therefore tested the hypothesis that the cells in the skin and lung have unique features. We found that primary human keratinocytes and bronchial epithelial cells were more dependent on T_H17 cytokines than other types of cell for the production of antistaphylococcal factors, including the neutrophil-recruiting chemokines and anti-bacterial peptides [44^{*}]. T-cells from HIES patients, despite having defects in the production of T_H17 cytokines, produced other proinflammatory cytokines, including IL-1 β and TNF α , in normal amounts. These cytokines were not sufficient to trigger antistaphylococcal factor production in keratinocytes and bronchial epithelial cells, but the production of these factors was induced in fibroblasts and endothelial cells. These findings provide a possible molecular explanation for the apparent paradox of systemic T_H17 deficiency in HIES patients with staphylococcal infections restricted to the skin and lungs. They also provide interesting insight into tissue-specific immunity. Epithelial cells are constantly exposed to environmental agents. They have evolved to respond only weakly to the

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first signal — the classical proinflammatory cytokines produced by innate immune cells — but respond more strongly to a combination of this first signal and a second signal provided by T-cells.

Antigen-specific antibody production

HIES patients have normal serum IgM, IgG, and IgA levels, but most have defects of various types in the antigen-specific antibody response to immunization [1]. They also suffer from infections with encapsulated bacteria [45–48]. IgG subclass deficiencies have been reported in some patients [1]. Most patients with HIES with *STAT3* mutations have smaller than normal numbers of circulating memory B cells [49].

Mice lacking *STAT3* expression in B cells display normal B-cell development, normal baseline serum antibody levels of IgM, IgG, and IgA and produce normal T-independent (TI) and T-dependent (TD) IgM, IgA, and IgE responses, but have defective TD IgG responses [50]. Germinal center formation, isotype switching, and the generation of memory B cells all occur normally in *STAT3*-deficient murine B cells. There are several possible reasons for the difference in phenotype between humans and mice: first human mutations are *dominant negative*, but not null; second, mutations in humans are expressed not only in B cells, but also in other cell types, with possible indirect effects on B-cell differentiation. Alternatively, there may be a species-specific difference in the requirement for *STAT3* between humans and mice.

Skeletal manifestations

STAT3 plays important roles in the differentiation of both osteoblasts and osteoclasts *in vitro*, and mice lacking *STAT3* in osteoblasts or osteoclasts have an osteoporotic phenotype [51,52]. In humans, osteoclasts generated from peripheral blood monocytes from HIES patients with *STAT3* mutations and display higher levels of bone-resorption activity than those from control subjects [12^{••}]. These observations are consistent with the osteoporosis observed in HIES patients, but it remains unclear why these patients also display the retention of deciduous teeth, which would be expected to result from the impairment of osteoclast activity.

Hyper-IgE-emia

Serum concentrations of IgE are extremely high in patients with HIES, usually at least a hundred times higher than those in normal individuals (>2000 IU/ml). The molecular mechanism of hyper-IgE-emia remains unknown. Murine IL-21 inhibits IgE production by B cells, but human IL-21 acts in synergy with IL-4 to upregulate IgE production [53]. Unlike IgG-producing plasma cells, IgE-producing plasma cells are excluded from the germinal center [54]. In the absence of Bcl-6, a transcriptional repressor required for germinal center formation, class-switching to IgE in response to IL-4 is

upregulated because of a loss of repression of IL-4/*STAT6* [55]. IL-21 may be involved in the trafficking of developing B cells in the germinal center [56–59]. IL-6/*STAT3* signaling promotes the differentiation of naive T-cells into helper T-cells capable of assisting B cells, in a process independent of follicular helper T-cell differentiation [60]. It is not yet clear how these pieces of the puzzle fit together to explain the extremely high serum IgE levels in HIES patients. This is clearly one of the most important unresolved issues and its resolution might open up new possibilities for regulating serum IgE levels in common atopic disorders.

Conclusion

In the past three years, we have witnessed major progress toward the identification of the molecular causes of HIES. The identification of a patient with *TYK2* deficiency revealed the critical functions of *TYK2* in the transduction of multiple cytokine signals involved in innate and acquired immunity, and demonstrated the greater importance of *TYK2* functions in humans than in mice. The identification of *TYK2* deficiency as an etiology of type 2 HIES led to the identification of *dominant-negative STAT3* mutations as a major molecular cause of type 1 HIES.

This discovery has improved our understanding of the crucial roles played by *STAT3* in protection against extracellular pathogens and Th17 cell differentiation. Studies of patients with HIES provide further evidence of the power of ‘experiments of nature’ for dissecting the complex human immune system. Answers to most of the unresolved questions will probably be found in the near future, providing further insight into the various aspects of the human immune system involved in HIES development. This progress should eventually lead to improvements in the treatment for patients.

Conflict of interest

The authors have no conflicting financial interests.

Acknowledgements

This work is supported by Grants-in-Aid 19390282, 20060009, and 21659253 from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and Research on Intractable Diseases from the Ministry of Health, Labor and Welfare, the Uehara Foundation, Naito Foundation, and the Mother and Child Health Foundation.

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