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Molecular mechanisms of the immunological abnormalities in hyper-IgE syndrome

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Hyper-IgE syndrome (HIES) is a primary immunodeficiency characterized by atopic dermatitis associated with extremely high serum IgE levels and susceptibility to staphylococcal skin abscesses and pneumonia. Recent studies have identified dominant negative mutations in the signal transducer and activator of transcription 3 gene (*STAT3*) as a major molecular cause of classical hyper-IgE syndrome, but the molecular mechanisms underlying this syndrome remain unclear. We recently showed that the impaired development of interleukin 17 (IL-17)–producing T helper cells (Th17 cells) due to defective IL-6 and IL-23 signaling in T cells, and the impaired generation of induced regulatory T (iT_{reg}) cells from defective IL-10 signaling in dendritic cells, may account for the immunological abnormalities of hyper-IgE syndrome. These findings open up possibilities for exploring new approaches to the treatment of HIES patients.

Keywords: Th17 cell; iTreg cell; staphylococcal infection; atopic dermatitis; *STAT3*

Introduction

Hyper-IgE syndrome (HIES) is a complex primary immunodeficiency disorder (PID) characterized by recurrent staphylococcal skin abscesses and pneumonia, atopic dermatitis, and extremely high serum IgE levels.^{1,2} Recent studies have demonstrated the multisystem nature of HIES,³ the signs of which are not restricted to the immune system, extend to skeletal and lung parenchymal abnormalities, such as osteoporosis, fracture with minor trauma, scoliosis, hyperextensive joints, retention of primary teeth, bronchiectasis, and pneumatocele. Dominant-negative mutations in *STAT3* have been identified as a major molecular cause of the multisystem HIES.^{4,5} However, our understanding of the molecular mechanism underlying this syndrome remains limited. In this review, we focus on the molecular mechanisms underlying immunological manifestations of HIES due to dominant negative mutations in *STAT3*.

STAT3

STAT3 plays a critical role in signal transduction for many cytokines and growth factors, including those of the γ c family (IL-2, IL-4, IL-7, IL-9, IL-15,

IL-21), the gp130 family (IL-6, IL-11, IL-27, IL-31), the IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29), and receptor-type tyrosine kinases (M-CSF, Flt-3, PDGF, EGF, FGF, GH, IGF) (Table 1).⁶ *STAT3* functions as a transcription factor, binding to promoter regions and initiating transcription of its target genes. *STAT3* mediates signaling for about 40 cytokines and growth factors. It is, therefore, not straightforward to determine which pathway, in which cell type is critical for the signs of HIES. Studies of a null mutation of the *STAT3* gene in mice demonstrated that *STAT3* was essential for embryo survival close to the time of implantation (E6.5–E7.5).⁷ Other studies of mice with a tissue-specific deletion of *STAT3* demonstrated the critical role of *STAT3* in cell survival, proliferation, migration, apoptosis, and inflammation in diverse cells including keratinocytes, hepatocytes, thymic epithelial cells, respiratory epithelial cells, neurons, lymphocytes, and macrophages.⁸ The multisystem signs in HIES patients probably reflect the diverse functions *in vivo* of *STAT3* in humans.

Th17 cells

Th17 cells—a subset of helper T cells producing cytokines including IL-17A, IL-17F, and IL-22—

Table 1. Ligands, receptors, and Jak family kinases upstream of STAT3

	Ligands		Receptors		Jak family kinases		
γ c family	IL-2	γ c	IL-2Ra	IL-2Rb	Jak1	Jak3	
	IL-4	γ c	IL-4Ra		Jak1	Jak3	
	IL-7	γ c	IL-7Ra		Jak1	Jak3	
	IL-9	γ c	IL-9Ra		Jak1	Jak3	
	IL-15	γ c	IL-15Ra	IL-2Rb	Jak1	Jak3	
	IL-21	γ c	IL-21R		Jak1	Jak3	
IFNs	IFN- α	IFNAR1	IFNAR2		Jak1	Tyk2	
	IFN- β	IFNAR1	IFNAR2		Jak1	Tyk2	
	IFN- γ	IFNGR1	IFNGR2		Jak1	Jak2	
IL-12/23	IL-12	IL-12Rb1	IL-12Rb2		Jak2	Tyk2	
	IL-23	IL-12Rb1	IL-23R		Jak2	Tyk2	
gp130 family	IL-6	gp130	IL-6Ra		Jak1	Jak2	Tyk2
	IL-11	gp130	IL-11Ra		Jak1	Jak2	Tyk2
	IL-27	gp130	IL-27Ra		Jak1	Jak3	
	IL-31	gp130	IL-31Ra		Jak1	Jak3	
	LIF	gp130	LIFR		Jak1	Jak3	
	OSM	gp130	OSMRb		Jak1	Jak3	
	CNTF	gp130	CNTFR		Jak1	Jak3	
	CT-1	gp130	CT-1R		Jak1	Jak3	
IL-10 family	IL-10	IL-10R2	IL-10R1		Jak1	Tyk2	
	IL-19	IL-20R1	IL-20R2		Jak1	Jak2	
	IL-20	IL-20R1	IL-20R2		Jak1	Jak2	
	IL-22	IL-10R2	IL-22R		Jak1	Tyk2	
	IL-24	IL-20R1	IL-20R2		Jak1	Jak2	
	IL-26	IL-10R2	IL-20R1		Jak1	Jak2	
	IL-28	IL-10R2	IL-28R1		Jak1	Tyk2	
	IL-29	IL-10R2	IL-28R1		Jak1	Tyk2	
Receptor type	M-CSF	M-CSFR			—		
	Flt3L	Flt3			—		
	PDGF	PDGFR			—		
	EGF	EGFR			—		
	FGF	FGFR			—		
	GH	GHR			—		
	IGF	IGFR			—		
Others	IL-5	β c	IL-5Ra		Jak1	Jak2	
	G-CSF	G-CSFR			Jak1	Jak2	Tyk2
	Leptin	LEPR			Jak2		
	PAF	PAFR			Jak2		

have been extensively studied as inducers of autoimmune disorders.^{9–13} Recent studies have also indicated that Th17 cells play a key role in host defense against extracellular bacteria and fungi.^{14,15} Interestingly, most staphylococcal and *Candida* infections occurring in patients with HIES are confined to the skin and lung, whereas in patients with chronic granulomatous disease—another human primary immunodeficiency—staphylococcal infections are frequently systemic.¹⁶ These clinical observations suggest that Th17 cytokines play an important role in host defense on the

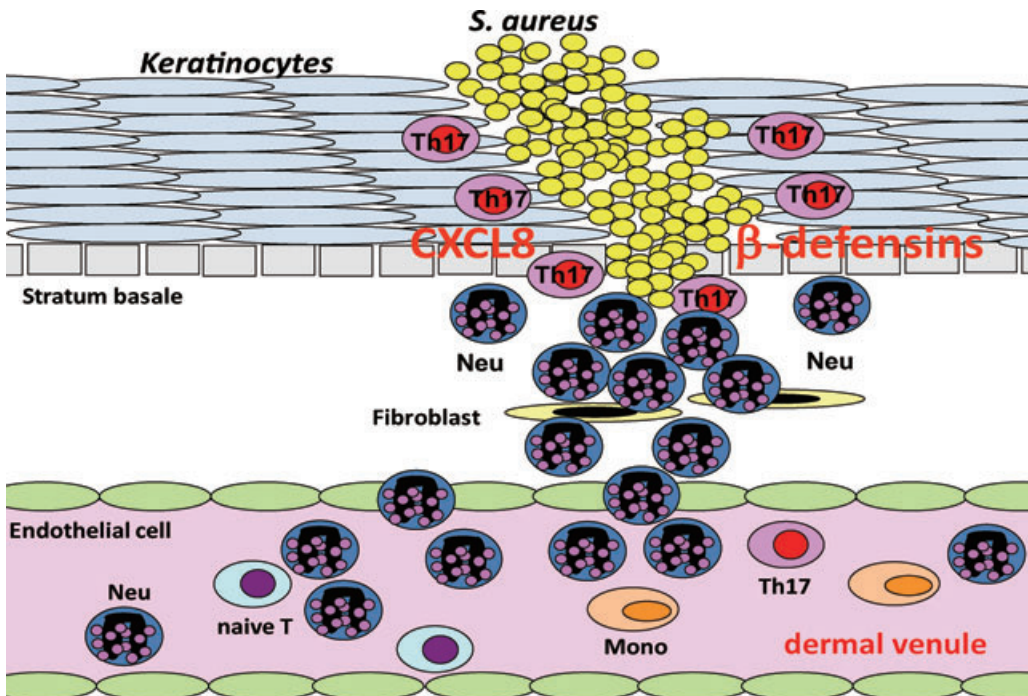


Figure 1. Protection against *Staphylococcus aureus* at the skin. The production of Th17 cytokines is severely decreased in HIES patients, which is required for the production of antimicrobial peptides, including β -defensin 2 and β -defensin 3, and neutrophil-recruiting chemokines, including CXCL8 (IL-8) from keratinocytes. The lack of antimicrobial peptides and neutrophil-recruiting chemokines may result in the susceptibility to staphylococcal infection in the skin.

surface of the body, particularly in the skin and airways.

Many reports have indicated that the production of Th17 cytokines, including IL-17A, IL-17E, and IL-22, by activated T cells from HIES patients is much lower than those from control individuals, whereas the production of other proinflammatory cytokines, including IFN- γ , IL-1 β , and TNF- α , is unaffected.^{17–21} Such findings raise the questions of why and how systemic Th17 cell defects lead to staphylococcal infections restricted to the skin and lungs.

Insight into these questions was provided by the experimental observation that while supernatant from activated T cells from normal subjects induce keratinocyte and bronchial epithelial cell production of neutrophil-recruiting chemokines and β -defensins, supernatant from activated T cells from STAT3-deficient patients does not.²¹ Human primary keratinocytes and bronchial epithelial cells do not produce sufficiently large amounts of neutrophil-recruiting chemokines and β -defensins in response to Th17 cytokines or classical proin-

flammatory cytokines.²¹ Further support for these findings was provided by the demonstration *in vitro* that neutralization of Th17 cytokines decreases the production of the chemokines and defensins.²¹ In contrast to those data, primary dermal fibroblasts and endothelial cells were found to respond equally well to T cell supernatants from HIES patients and controls. Thus, keratinocytes and bronchial epithelial cells respond differently from other types of cells (e.g., fibroblasts and endothelial cells) to Th17 cytokines, with Th17 cytokines playing a more important role in the production of chemokines and β -defensins in epithelial cells. One interpretation of this observation is that epithelial cells are always exposed to external stimuli and therefore have developed a system that is unresponsive to a single stimulation (such as Th17 cytokines) yet are responsive to combinations of stimulations. By contrast, internal cells, including fibroblasts and endothelial cells, must respond to single stimuli more rapidly because such first signals are often indicative of pathogen invasion, which requires an immediate response.

These previously published data²¹ strongly indicate that Th17 cytokines play a crucial role in human host defense against *Staphylococcus aureus*, particularly at the surface barriers of the body (Fig. 1). Systemic T cell defects are converted into local defects, because only keratinocytes and bronchial epithelial cells require cytokines produced by Th17 cells in order to secrete neutrophil-recruiting chemokines and antimicrobial peptides. These findings provide at least a partial explanation for the restriction of staphylococcal infections to the skin and lungs of HIES patients and highlight the physiological role of Th17 cytokines in protection against extracellular pathogens in humans.²¹

Induced regulatory T cells

One of the potential mechanisms of atopic dermatitis development in HIES is an acceleration of Th2 cell activity.^{22–24} Effector Th2 cells are considered to be the major cell type that responds to allergens and produces Th2 cytokines, including IL-4, IL-5, IL-9, and IL-13. These Th2 cytokines induce changes in blood vessels, upregulate adhesion molecules, and recruit eosinophils. Th2 cytokines also induce class switching to IgE.²⁵ Recently identified cytokines such as IL-25, IL-31, and IL-33 also participate in Th2 cell-mediated inflammatory diseases.^{26–28} In addition to Th2 cells, Th1 cells play a role in the pathogenesis of atopic dermatitis—contributing at a later time point—by inducing the apoptosis of epithelial cells.²⁹

Another potential mechanism by which atopic dermatitis may develop in HIES patients is by impairment of regulatory T (T_{reg}) cell activity; T_{reg} cells are key mediators of peripheral tolerance that suppress effector Th2 cells. The transcription factor Foxp3 is an important regulator of the development, function, and survival of T_{reg} cells, as clearly demonstrated by primary immunodeficiency in which patients lack FOXP3 gene expression and present with severe autoimmune and atopic phenotypes. Mutations in the human FOXP3 gene (*FOXP3*) result in immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome.^{30,31} Foxp3 deficiency in mice also leads to atopic phenotypes.^{32,33}

There are at least two types of Foxp3⁺ T_{reg} cells: natural T_{reg} (n T_{reg}) cells and induced T_{reg} (iT $_{reg}$) cells. Natural T_{reg} cells develop in the thymus, whereas iT $_{reg}$ cells develop in the periphery. TGF- β

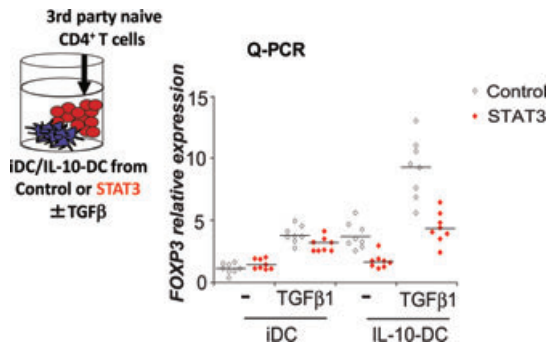


Figure 2. Q-PCR analysis of relative *FOXP3* mRNA expression (FOXP3/HPRT) after the co-culture of third-party allogeneic naive CD4⁺ T cells from a control subject with untreated immature DCs (iDCs) or IL-10-DCs from eight controls and eight *STAT3* patients in the absence or presence of exogenous TGF- β 1. IL-10-DCs upregulate *FOXP3* expression as efficiently as TGF- β 1 and the combination of IL-10-DCs and TGF- β synergistically upregulates the expression of *FOXP3*.

plays a crucial role in the induction of iT $_{reg}$ cells; its expression in the presence of TCR stimulation converts naive Foxp3⁻CD4⁺ T cells into Foxp3⁺ iT $_{reg}$ cells.^{34–37} In addition to soluble factors, dendritic cells play a key role in the induction of T_{reg} cells.^{38,39}

It has been shown that dendritic cells of patients with HIES display defective IL-10 signaling, which results in impaired suppression of cytokine production and T cell proliferation. In addition, dendritic cells from HIES patients are defective in generating Foxp3⁺ iT $_{reg}$ cells by IL-10 treatment.⁴⁰ Defective generation of iT $_{reg}$ cells in response to IL-10 has also been observed in the other form of HIES that results from TYK2 deficiency.⁴¹

In terms of the molecular mechanisms involved, IL-10 normally upregulates the expression of PD-L1 and ILT-4 on the surface of dendritic cells, and both of these molecules are required for the induction of Foxp3⁺ iT $_{reg}$ cells.⁴⁰ In addition, IL-10-treated dendritic cells induce iT $_{reg}$ cells as efficiently as does TGF- β , and the combination of IL-10-treated dendritic cells and TGF- β synergistically induces iT $_{reg}$ cells (Fig. 2). Both of these IL-10-mediated pathways are likely defective in HIES patients. IL-10 signaling in dendritic cells is crucial for generating iT $_{reg}$ cells *in vivo* and thus for maintaining an appropriate Th2– T_{reg} cell balance to prevent hyper-IgE syndrome.

Many studies have suggested that IL-10 is one of the key regulators of atopic dermatitis. The exposure of the skin to allergens induces allergen-specific unresponsiveness due to the production of IL-10^{42,43} that modulates Langerhans cells and dermal dendritic cells to induce allergen-specific tolerance. A defect in IL-10-mediated tolerance to innocuous environmental antigens may thus be one of the mechanisms underlying the atopic dermatitis in hyper-IgE syndrome. Indeed, in humans it has been shown that low IL-10 is involved in the molecular pathogenesis of atopic disorders; the frequency of allergen-specific, IL-10-secreting T cells is significantly higher in nonatopic individuals than in atopic patients;⁴⁴ and IL-10 levels are inversely correlated with the severity of human allergic diseases.^{45,46} Also, effective allergen-specific immunotherapies increase IL-10 synthesis by T cells.^{47,48}

In rodent studies, mice lacking IL-10 or the IL-10 receptor spontaneously develop inflammation in the large intestine,^{49–51} and mice with T_{reg} cell-specific IL-10 deficiency also display inflammation of body surfaces that are in contact with the environment, such as the colon, lungs, and skin.⁵² In humans, mutations in the genes encoding IL-10 or IL-10 receptor subunits have been found in patients with early-onset enterocolitis.⁵³

HIES patients, however, do not display a marked increase in the frequency of enterocolitis despite the impairment of IL-10 signaling, which may reflect partial IL-10 signaling. In addition to this IL-10 signaling defect, patients with STAT3 mutations have defective Th17 cell development. Thus, the combination of Th17 cell deficiency and an IL-10 signaling defect may prevent the development of enterocolitis but induce atopic dermatitis in HIES patients.⁵⁴

Naive CD4⁺ T cells educated by IL-10-treated dendritic cells have antigen-specific iT_{reg} activity.⁵⁵ A previous study showed that the generation of FOXP3⁺ iT_{reg} cells by IL-10-treated dendritic cells is impaired in HIES patients.⁴⁰ Because T_{reg} cells mediate peripheral tolerance and play a central role in determining several immune diseases, including autoimmunity, chronic infections, tumors, and allergies,⁵⁶ FOXP3⁺ T_{reg} cells are likely involved in protecting humans against allergic diseases, as patients with IPEX syndrome suffer from allergic symptoms. Consistent with this, peripheral blood

mononuclear cells (PBMCs) from atopic patients proliferate more extensively and produce more Th2 cytokines in response to allergen than do PBMCs from nonatopic healthy individuals.⁵⁷ However, patients with atopic dermatitis have normal numbers of T_{reg} cells in the periphery—likely nT_{reg} cells—with normal suppressive activity.⁵⁸ Such results suggest that iT_{reg} cells may be more important than nT_{reg} cells for controlling atopic dermatitis. Indeed, a recent study in two mouse strains—one capable of generating iT_{reg} cells but not nT_{reg} cells and the other unable to generate either iT_{reg} or nT_{reg} cells—suggested that iT_{reg} cells control allergic inflammation in response to innocuous environmental allergens, whereas nT_{reg} cells do not.⁵⁹

Therapeutic implications

Some patients with HIES are doing well with conventional treatments, but the other patients suffer from severe clinical manifestations, such as early-onset pneumonia and subsequent pneumatocele formation, which is further complicated by multidrug-resistant *Pseudomonas* and *Aspergillus* infections. A significant number of patients in their twenties die of pulmonary hemorrhage due to fungal vascular invasion and brain metastasis of fungal disease.⁶⁰ At present, it is not clear that this diversity of clinical courses is caused by environmental or genetic factors. Previous studies suggested that the molecular mechanisms underlying the immunological manifestations of HIES, including staphylococcal pneumonia are likely to be caused by T cell defects, and that these defects could be corrected by stem cell transplantation. Future studies need to identify a subgroup of HIES patients with poor prognosis, which will provide an opportunity to improve clinical outcome by early stem cell transplantation before the onset of severe infections and parenchymal lung sequelae. Furthermore, stem cell transplantation might be beneficial for some HIES patients even after the episodes of pneumonia and parenchymal lung complications.

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Conflicts of interest

The authors declare no conflicts of interest.

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