Brief Reviews

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Insights into the Role of STAT3 in Human Lymphocyte Differentiation as Revealed by the Hyper-IgE Syndrome[1]

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"Experiments of nature" due to single gene mutations resulting in human immunodeficiency states have revealed critical roles for several genes in regulating lymphocyte development and the generation of protective immunity. Recently, heterozygous mutations in *STAT3* were found to cause autosomal dominant hyper-IgE syndrome, a condition affecting not only the immune system but also other mesenchymal and ectodermal tissues, including bones, cranium, teeth, and skin. STAT proteins operate to integrate signals from surface receptors, including cytokine receptors, that regulate growth and differentiation of multiple cell lineages. In this article, we will review how the study of STAT3 deficiency in humans and mice has highlighted nonredundant roles of STAT3, and of specific cytokines, in diverse cellular processes such as antimicrobial immunity and protection at epithelial barriers, the generation of functional humoral immune responses, bone formation, and keratinocyte biology. ***The Journal of Immunology,*** **2009, 182: 21–28.**

Cytokines, including ILs, IFNs, and CSFs, exert pleiotropic effects on the development and differentiation of multiple cell lineages. Cytokine-induced signal transduction is mediated by JAK/STAT proteins and is regulated by the suppressor of cytokine signaling (SOCS)[4] family of proteins. JAKs associate with the cytoplasmic domains of multimeric cytokine receptors and, following engagement by specific ligands, become activated and phosphorylate specific cytoplasmic tyrosine residues that act as docking sites for STAT proteins. Receptor-associated STAT proteins undergo JAK-mediated tyrosine phosphorylation and then form dimers that are translocated to the nucleus where they bind specific DNA sequences that promote transcription of target genes (1, 2). Cytokines control their own biological effects by inducing expression of specific SOCS proteins that act via a negative feedback loop to attenuate cytokine signaling (3, 4).

The STAT family is highly conserved and has been co-opted in various developmental pathways in different species. Currently, four mammalian JAKs (JAK1, JAK2, JAK3, Tyk2) and seven STATs (STAT1, 2, 3, 4, 5a, 5b, 6) have been identified (1–4). Analysis of gene-targeted mice has revealed critical roles for STATs in hematopoietic and nonhematopoietic lineages (reviewed in Refs. 1 and 2). Furthermore, mutations in *Tyk2*, *JAK3*, *STAT1*, and *STAT5b* cause human immunodeficiencies (5–8) (see Table I), thus highlighting the fundamental requirement for intact JAK/STAT pathways in many biological systems. Most recently, *STAT3* mutations have been found to cause autosomal dominant (AD) hyper-IgE syndrome (HIES; AD-HIES) (9, 10) (Table I). We will review STAT3-deficient mice and clinical aspects of AD-HIES to reveal the specific functions of STAT3 in generating protective cellular and humoral immune responses to different pathogens. The role of SOCS proteins in negatively regulating cytokine signaling has recently been reviewed (3, 4) and thus will not be covered here.

Elucidation of the role of STAT3 in hematopoietic cells by the generation of gene-deficient mice

STAT3 has been implicated in the signal transduction pathway of multiple cytokines, including the IL-2/γc (IL-2, IL-7, IL-9, IL-15, IL-21), IL-6/gp130 (IL-6, IL-11, IL-27, IL-31, ciliary neurotropic factor, oncostatin M, and leukemia inhibitory factor), IFN (IFN-γ, IFN-α/β) and IL-10 (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26) families of cytokines, as well as IL-12, IL-23, Flt3 ligand, M-CSF, G-CSF, leptin, and growth hormone (3–5, 11–16). Given the broad function of STAT3 in many cell types, it is perhaps not surprising that germline deletion of STAT3 is embryonically lethal (17) due to a requirement of STAT3-dependent signaling downstream of leukemia inhibitory factor during trophoblast invasion and subsequent placental development (16). Subsequently, mice lacking STAT3

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[4] Abbreviations used in this paper: SOCS, suppressor of cytokine signaling; AD, autosomal dominant; AR, autosomal recessive; DC, dendritic cell; HIES, hyper-IgE syndrome; PC, plasma cell; ROR, retinoic acid-related orphan nuclear receptor.

Table I. *Genetic lesions causing human immunodeficiency*

Mutated Gene	Disease Manifestation	Cytokines Involved	Reference
Jak3	SCID	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	6
Tyk2[a]	AR-HIES	Type I IFNs, IL-6, IL-10, IL-12, IL-23	7
STAT1	Mendelian susceptibility to mycobacterial disease	Type I and II IFNs	Reviewed in 5
STAT3	AD-HIES	IL-6, IL-10 and IFN families, IL-21, IL-23, plus others	9, 10
STAT5b	T- and NK-cell lymphopenia, immunodeficiency	IL-2 plus others	8

[a] Although a *Tyk2* mutation has been reported in one AR-HIES patient (7), it is unlikely that such mutations are responsible for disease in the majority of these individuals (53).

expression in specific cell lineages have shed light on the pivotal role of STAT3 in $CD4^+$ T cells, B cells, myeloid cells, and granulocytes (Table II).

$CD4^+$ T cells

The first lineage-specific deletion of STAT3 was in $CD4^+$ T cells, which revealed impaired proliferation in response to IL-6 and, to a lesser extent, IL-2 (11). Despite these early findings, a specific function for STAT3 in normal immunity only emerged once the specification of memory/effector T cell subsets was elucidated. Th17 cells are a recently described lineage of $CD4^+$ T cells characterized by the production of a unique set of effector molecules (e.g., IL-17A, IL-17F, IL-21, IL-22, IL-26, CCL20) that play important roles in immunity against extracellular pathogens (18–20). Protection is largely mediated by inducing granulopoiesis, recruitment, expansion, and activation of neutrophils and by stimulating immune defense mechanisms at epithelial barriers (Fig. 1*a*) (19). In addition to this protective role, Th17 cells have been implicated in autoimmune diseases in humans (rheumatoid arthritis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis), and corresponding murine models (experimental autoimmune encephalomyelitis, collagen-induced arthritis, inflammatory bowel disease) (18–20). The commitment of murine naive $CD4^+$ T cells to the Th17 lineage requires TGF-β and IL-6 (21, 22). However, other cytokines contribute to the generation of murine Th17 cells, either by enhancing the effects of TGF-β/IL-6 (TNF-α, IL-1β) or by maintaining established Th17 cells (IL-23; Fig. 1*a*) (18, 19, 21, 23). Similarly, IL-21 can substitute for IL-6 in the generation of murine Th17 cells and act as an autocrine growth factor for these cells (24–27). Despite these findings, recent data have questioned whether IL-21 plays any role in the establishment or function of Th17 cells in vivo (28). Because the original studies of STAT3 in $CD4^+$ T cells predated the discovery of Th17 cells, a specific role for STAT3 went unrecognized for nearly a decade. However, it is now well established that STAT3 is necessary for the generation of Th17 cells (29–31). STAT3 achieves this by binding to the promoters and inducing expression of the cytokines IL-17A, IL-17F (32), and IL-21 (27), as well as the retinoic acid-related orphan nuclear receptors (RORs) RORγt and RORα, both of which are required for naive murine $CD4^+$ Th17 cell differentiation (29, 33, 34) (Fig. 1*a*). This is consistent with the ability of IL-6 and IL-23 (and IL-21) to activate STAT3 and with the likely roles of these cytokines in generating and maintaining Th17 cells (Fig. 1*a*) (4). Recent studies have also revealed that STAT3 deficiency abrogates the ability of IL-6 and IL-27 to induce production of IL-10 by $CD4^+$ T cells (15). It will be important to determine whether impaired IL-10 production has any immunopathological effects in mice lacking STAT3 in their $CD4^+$ T cells.

Table II. *Effects of STAT3 deficiency on Cellular Function*

Cell Type	Defect	Human	Mice	Cytokine(s) Likely Responsible	Reference
CD4+ T cells	Th17 deficiency	Yes	Yes	IL-6, IL-21, IL-23	29 (mouse); 54–57 (human)
	Impaired IL-10 production	Yes	Yes	IL-6, IL-27 (mouse)	15 (mouse); 55 (human)
B cells	Lack of Ag-specific PC	Inferred from functional Ab deficiencyin AD-HIES	Yes	IL-6, IL-21 (mouse); IL-6, IL-10, IL-21 (human)	35 (mouse); 45, 49–51 (human)
Myeloid cells	Excessive production of proinflammatory cytokines, chemokines	Not examined	Yes	IL-10	12 (mouse)
Dendritic cells	Impaired development	Not examined	Yes	Flt3 ligand	13 (mouse)
Keratinocytes	Alopecia, dermatitis, skin ulcers	Inferred from AD-HIES	Yes	IL-22	62 (mouse)
Osteoclasts and monocytes	Increased bone resorption	Yes	Yes	IL-6 family	77 (mouse); 75 (human)

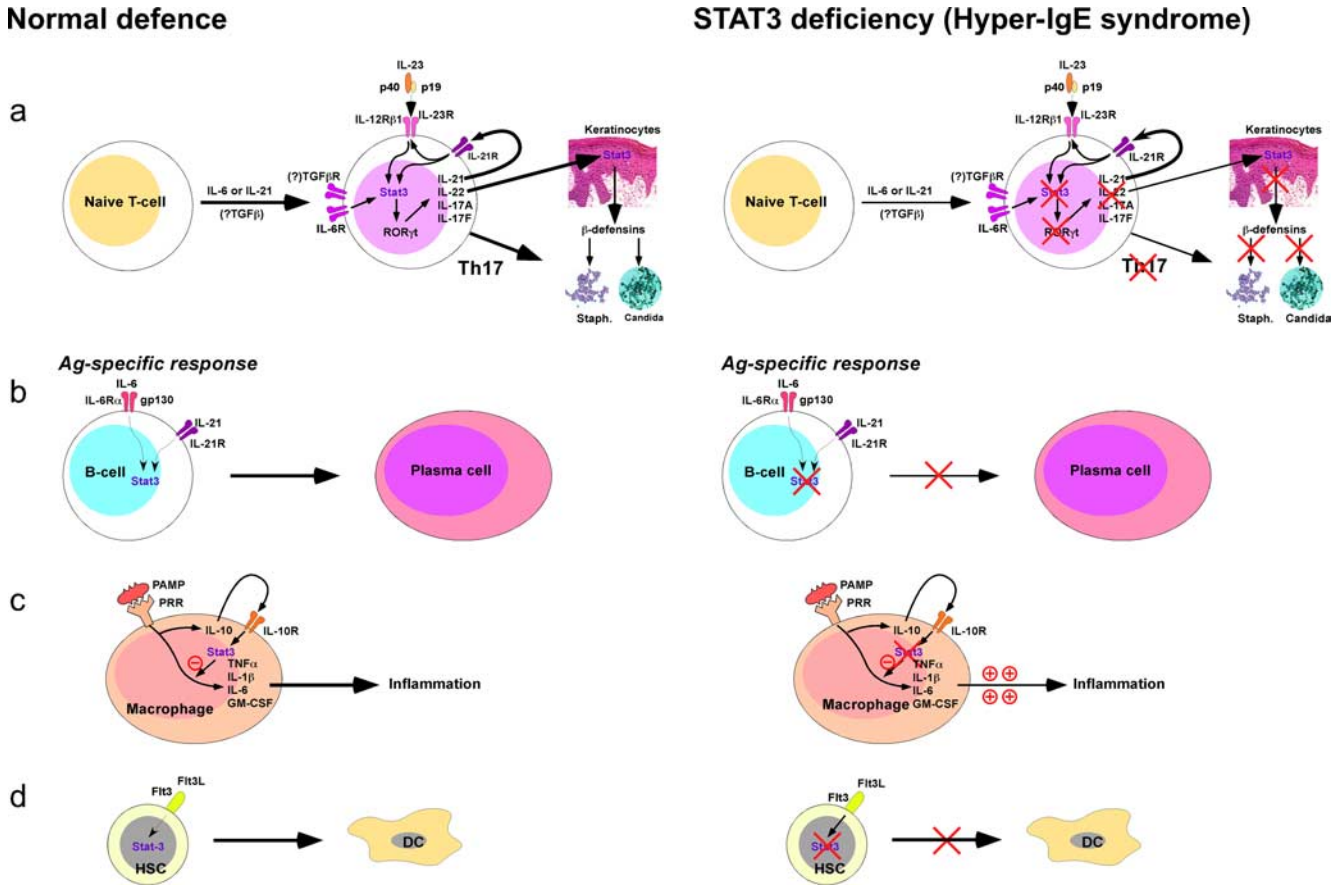

FIGURE 1. Roles of STAT3 in the differentiation and acquisition of the effector function of lymphoid and myeloid cells and the consequences of *STAT3* mutations. *a*, Differentiation of Th17 cells. Initial generation requires IL-6 or IL-21, whereas expansion or maintenance of these cells requires IL-21 and IL-23. Impaired generation of Th17 cells in AD-HIES and subsequent defects in host defense against extracellular bacteria highlight the role of STAT3 as a signaling protein distal to these cytokines and its critical function in Th17 cell function. Note: although TGF-β is depicted as having a role in generating Th17 cells, this remains controversial for human CD4$^+$ T cells. Staph, *Staphylococcus*. *b*, Plasma cells. Mice lacking expression of STAT3 in B cells are unable to elicit specific IgG responses to T cell-dependent Ag. This resembles the absence of functional Ab responses in AD-HIES and probably reflects impaired signaling by the STAT3-activating cytokines IL-6 and IL-21 (as well as IL-10 in humans). *c*, Myeloid cells. Mice lacking expression of STAT3 in myeloid cells and granulocytes develop inflammatory bowel disease-type inflammation due to a lack of IL-10-mediated immune regulation, which acts to suppress the action of many proinflammatory cytokines produced by these cells. Note: conditional deletion of STAT3 from CD4$^+$ T cells also impairs their production of IL-10 (15). How this contributes to dysregulated inflammatory conditions remains to be determined. PAMP, Pathogen-associated molecular pattern; PRR, pattern recognition receptor. *d*, Dendritic cells. Flt3 ligand is required for the generation of all lineages of dendritic cells from hematopoietic stem cells (HSC) in mice. Dendritic cell development in humans with *STAT3* mutations remains to be thoroughly investigated.

B cells

Mice lacking STAT3 in B cells exhibit normal B cell development, have normal levels of serum IgM, IgG, and IgA, and produce normal levels of specific IgM following immunization with T cell-dependent Ag (35). However, B cell STAT3 deficiency renders mice incapable of generating a T cell-dependent IgG response (Fig. 1*b*) (35). The paucity of IgG-secreting plasma cells (PCs) did not result from a defect in germinal center formation nor isotype switching, as these processes were evident in B cell STAT3-deficient mice (35). Although it is well established that the transcription factors Blimp-1 and XBP-1 are required for B cells to differentiate to the PC lineage (36), Fornek and colleagues proposed that these transcription factors were insufficient for the generation of all PCs, with STAT3 and by inference a STAT3-activating cytokine being requisite for IgG-PC (35). Possible candidates for this in mice are IL-6 and IL-21 (Fig. 1*b*), because mice transgenic for either cytokine exhibit increased serum levels of IgG1, whereas IL-21R-deficient mice have dramatic reductions in levels of total and Ag-specific serum IgG1 (37, 38).

Macrophages and granulocytes

A major function of macrophages and neutrophils is to produce proinflammatory cytokines that mediate early responses to infectious organisms. Proinflammatory factors including TNF-α, IL-1β, IL-6, GM-CSF, and reactive oxygen species can cause significant tissue damage, suggesting a requirement for strict regulation of innate immune cells. One counter-regulatory mechanism is autocrine production of IL-10 by myeloid cells, which acts in a feedback loop to inhibit production of proinflammatory mediators (39, 40). Production of proinflammatory cytokines by activated monocytes precedes that of IL-10, thereby allowing sufficient time for proinflammatory cytokines to exert their effect before being attenuated by IL-10 (39). Because IL-10R signals through STAT3 (14, 40), an important consequence of eliminating STAT3 from macrophages/granulocytes is the loss of IL-10-mediated suppression of the proinflammatory actions of these cells (Fig. 1*c*) (12). Thus, mice lacking STAT3 in macrophages/granulocytes acquired exquisite sensitivity to endotoxic shock due to exacerbated production of TNF-α, IL-6, and IL-1β by macrophages and IFN-γ by CD4$^+$

T cells. Consequently, $CD4^+$ T cell differentiation is skewed toward the Th1 lineage, resulting in chronic enterocolitis resembling Crohn's disease (12). Furthermore, increased trafficking of effector leukocytes into inflamed tissues occurs due to excessive production of macrophage-recruiting chemokines (41). The similarities between macrophage/granulocyte STAT3-deficient and IL-10-deficient mice with respect to inflammatory bowel disease (12, 42) highlighted the fundamental requirement for STAT3 in IL-10-mediated suppression of the potent proinflammatory activities of myeloid and granulocytic cells (Fig. 1*c*).

Dendritic cells (DCs)

A well-characterized regulator of DC development is Flt3 ligand (43). Mice lacking hematopoietic cell expression of STAT3 developed ~10-fold fewer DC than control mice, while the development of lymphocytes was unaffected (13). Although treatment of intact mice with exogenous Flt3L increased splenic DCs ~30-fold, the effect on DC precursors in STAT3-deficient mice was negligible (13). This study elegantly demonstrated that STAT3 is indispensable for Flt3L-mediated development of DC (Fig. 1*d*).

HIES

An historical overview. The first cases of HIES were reported in 1966 (44) in two red-haired girls with childhood eczema complicated by recurrent "cold" staphylococcal abscesses of the skin and lymph nodes, chronic otitis media and sinusitis, and recurrent staphylococcal pneumonia. Despite invasive mucosal and epithelial infections, systemic dissemination was not a feature. The constellation of clinical features arising from the "defect in local resistance to staphylococcal infections" was named Job's syndrome. After the discovery of IgE and its measurement in diagnostic laboratories, Buckley et al. (45) described the association between similar clinical manifestations, this time in two boys, and extreme elevations of IgE. This report also noted the coarse facial appearance of affected children and poor functional Ab and cellular responses to vaccination.

Clinical features. Great progress has since been made in defining the HIES phenotype. The classical triad comprises eczema from birth, recurrent staphylococcal skin and lung abscesses, and marked elevation of serum IgE (46–48). Patients typically develop neonatal eczematous rash complicated by recurrent staphylococcal boils and lymphadenitis secondary to *Streptococcus pneumoniae* and *Haemophilus influenzae* infection. Staphylococcal pneumonia is usually complicated by abnormal tissue repair resulting in the formation of air-filled sacs (pneumatoceles). Patients are susceptible to infection of the nails, skin, and mucosae with *Candida albicans* and other fungal pathogens, a susceptibility exacerbated by mechanical lung disruptions from prior infection that form a nidus for *Aspergillus* infection. Skeletal manifestations include joint hyperextensibility, short stature, coarse facial features, hypertelorism, osteopenia with fracture susceptibility, craniosynostosis, degenerative joint disease, and failure to shed primary teeth (44–46, 48). Laboratory investigation reveal near-normal levels of IgG, IgA, and IgM, but IgE frequently exceeds 2000 IU/ml (47, 49–51). Specific IgE to common allergens is often positive, suggesting that at least a component of IgE is Ag driven. Eosinophilia is almost always present. Functional Ab responses are variably impaired (47, 50, 51). Thus, HIES has a complex phenotype encompassing specific immune deficiency (susceptibility to infections), immune dysregulation (hyper IgE, impaired Ag-specific Ab formation), and abnormalities of the skin, skeleton, and teeth.

Autosomal dominant and recessive forms of HIES. Clear definition of the clinical syndrome has uncovered two major subtypes of HIES. The phenotype described above is typical of AD-HIES (46), whereas an autosomal recessive (AR) version has also been described (AR-HIES) (52). The phenotype of AR-HIES overlaps with AD-HIES — eczema, staphylococcal infections, elevated IgE, eosinophilia — but is distinguished by increased susceptibility to viral infections, autoimmunity, and CNS disease. Furthermore, lung infections heal without pneumatoceles, and skeletal/dental complications are absent. A single case of AR-HIES was found to result from homozygous null mutations in *TYK2* (7); however, the defect responsible for AR-HIES in other patients has not been elucidated (53).

Mutations in STAT3 are responsible for AD-HIES. In 2007, two groups independently identified heterozygous mutations in *STAT3* as the cause of AD-HIES (9, 10), including in one of the original patients described in 1966 (44). The vast majority of patients have mutations affecting the DNA-binding or Src homology 2 domains of STAT3 (9, 10, 54–57); however, mutations have recently been detected in the linker and transactivation domains (56, 57). The mutations are missense or in-frame microdeletions resulting in expression of a full-length but dysfunctional protein. Because the mutations are heterozygous, the STAT3 protein encoded by the alternate allele is normal. Thus, when STAT3 homodimers form in cells of patients with AD-HIES, the mutant protein acts as a dominant negative, resulting in ~75% of dimers lacking function. Indeed, while mutations in the DNA-binding domain do not affect protein expression, the ability of STAT3 to become tyrosine phosphorylated or to homodimerize with wild-type STAT3, the DNA-binding activity of wild-type/mutant and mutant/mutant but not wild-type/wild-type STAT3 dimers was diminished (9). In contrast to loss-of-function mutations in the DNA-binding domain, it is unclear how mutations in other domains of STAT3 affect its biological function. Despite having major clinical effects, the residual (i.e., ~25%) STAT3 activity resulting from the action of the wild-type/wild-type STAT3 dimers is sufficient to ensure viability of the fetus.

Impaired Th17 responses contribute to infection susceptibility of HIES patients

The discovery of *STAT3* mutations in AD-HIES led to questions of how impaired STAT3 function translates to susceptibility to infection. Because the Th17 differentiation factors IL-6, IL-21, and IL-23 all activate STAT3 (4, 18, 19), and STAT3 is required for Th17 lineage development in mice (29), several groups (54–57) investigated Th17 differentiation in AD-HIES. These studies revealed a marked impairment in the ability to generate Th17 cells in vivo and in vitro, evidenced by a failure to up-regulate RORγt, secrete IL-17 and IL-22, and generate Ag-specific Th17 cells in response to pathogens that characterize the immune susceptibility of patients with HIES (54) (Table II).

These data mirror murine studies showing a link between Th17 and mucosal immune protection, because IL-17AR deficiency and IL-22 blockade increased susceptibility to *Candida*, *Klebsiella* pneumonia and other extracellular bacteria, which correlated with impaired neutrophil mobilization (19, 58, 59).

These data suggest that STAT3 mutations inhibit Th17 differentiation and render HIES patients susceptible to specific pathogens. They also confirm the importance of human Th17 cells in response to *Candida* (60) and predict a role in defense against *Klebsiella* infection. Furthermore, AD-HIES provides a human model for the protective function of Th17 cells in vivo and suggests that Th17 deficiency could account for mucocutaneous candidiasis in other contexts, such as HIV/AIDS and iatrogenic immunosuppression.

As noted in the earliest reports, the burden of infection in AD-HIES is borne most heavily at epithelial surfaces. This could be accounted for by the role of STAT3 in mediating keratinocyte responses to IL-22 and oncostatin M that induce β-defensins, chemokines, and proinflammatory molecules important for immune protection in the skin and lungs in a STAT3-dependent manner (Fig. 1*a*) (19, 20, 61). Furthermore, IL-22-induced production of these mediators by epithelia is augmented by IL-17 (19, 20). Thus, consequences of a defect in Th17 cytokines would be amplified on epithelia, where STAT3 mutations compromise the IL-22-mediated induction and effector phases of the host response (Fig. 1*a*). Indeed, mice lacking STAT3 in keratinocytes develop alopecia, dermatitis, and skin ulceration (62), demonstrating that STAT3 mediates signals crucial for skin homeostasis by contributing to wound healing, keratinocyte proliferation, and maintaining the structural integrity of the epithelial barrier (62). These processes are likely mediated by IL-22 activating STAT3 (19, 63), which probably explains the chronic skin conditions in AD-HIES and the tendency to develop pneumatoceles during recovery from infection (Table II).

These studies of human Th17 cells in patients with STAT3-deficiency have contributed to the debate regarding the roles of specific cytokines in the generation of human Th17 cells. Despite general agreement on the specific requirements for the generation (i.e., TGF-β/IL-6) and maintenance (i.e., IL-23) of murine Th17 cells, there exists a great deal of controversy regarding the factors required for the differentiation of human $CD4^+$ T cells to the Th17 lineage. Initial reports found that IL-23 alone (64, 65) or IL-1β together with IL-6 (66) were sufficient for the differentiation of human naive $CD4^+$ T cells into Th17 cells. However, these studies have been contradicted by more recent findings that propose a central requirement for TGF-β in this process, at least in vitro (67, 68). The absence of Th17 cells from AD-HIES patients revealed an absolute requirement for STAT3 and, by inference, a STAT3-activating cytokine in the in vivo generation of human Th17 cells. Interestingly, patients with loss-of function mutations in IRAK4 or MyD88 (which are necessary components of the IL-1/IL-1R pathway) or gain-of-function mutations in TGF-β receptor had normal numbers of Th17 cells (56). If TGF-β is critical for the generation of human Th17 cells, it may be expected that these latter patients would have more Th17 cells than healthy controls. Thus, although TGF-β and IL-1β can both contribute to the in vitro generation of human Th17 cells from naive precursors (66–68), signaling through their receptors is not required in vivo. In contrast, patients with loss-of-function mutations in *IL-12RB1*, which is a component of the IL-12R and IL-23R, have fewer Th17 cells than healthy controls but more than AD-HIES STAT3-deficient patients (56). This report infers that IL-23 and another STAT3-activating cytokine, most likely IL-6, act in concert to induce Th17 cell differentiation in vivo.

Proposed mechanisms underlying other clinical features of AD-HIES

Although loss of Th17 cells in HIES explains some aspects of immune dysfunction, other aspects remain to be explained. However, it is possible to make some predictions based on the phenotypes of STAT3-deficient mice that could be examined experimentally using cells from *STAT3* mutant individuals (Table II).

Eosinophilia. Modulating IL-17 levels in a murine model of allergic asthma revealed that IL-17 suppressed eosinophil migration and recruitment into lung tissue by inhibiting production of pulmonary chemokines (69). Similarly, a lack of responsiveness of STAT3-deficient myeloid cells to IL-10 results in increased production of several chemokines (41). Thus, excessive production of eosinophil-tropic chemokines due to an absence of regulation by IL-17 (i.e., Th17 cells) (69) or IL-10 (41) may contribute to the eosinophilia that characterizes AD-HIES.

Functional Ab deficiency. Poor specific humoral immune responses have been documented in HIES (45, 49–51). This resembles B cell STAT3-deficient mice, which do not mount Ag-specific T cell-dependent IgG responses (35). The STAT3-activating cytokines IL-10 and IL-21 induce differentiation of human B cells into Ab-secreting cells (38, 70–72), whereas IL-6 promotes survival of PCs (73). Thus, impaired STAT3 signaling downstream of IL-6R, IL-10R, and IL-21R may underlie the deficiency in Ag-specific Ab responses in AD-HIES (Fig. 1*b*).

Although most assessments of humoral responses in AD-HIES patients focused on Ag-specific IgG (47, 50, 51), these patients also exhibit reduced levels of specific IgA in their serum and saliva (49). Because mice lacking IL-6 have impaired mucosal IgA immune responses (74), and IL-10 and IL-21 can induce IgA secretion by activated human B cells (70–72), it is likely that the generation of IgA-PC is also STAT3 dependent. However, it cannot be overlooked that, despite an absence of Ag-specific Ab responses, both AD-HIES patients (47, 49–51) and B cell STAT3-deficient mice (35) paradoxically have normal levels of total serum Ig (except IgE). Thus, there are clearly STAT3-independent mechanisms that contribute to basal Ig production that may be important in host protection against certain pathogens.

Defects in bone development. AD-HIES is associated with several skeletal defects: osteoporosis, short stature, mild facial dysmorphism, and craniosynostosis (47, 48). Possible contributing factors include defects in the actions of bone-producing osteoblasts and bone-resorbing osteoclasts, altered activity of monocytes, and defects in bone differentiation, especially within cranial sutures. An early study of HIES patients revealed an increased ability of their monocytes to resorb bone compared with controls (75). Interestingly, TNF-α and IL-1β can stimulate monocyte-mediated bone resorption (76). Because STAT3-deficient murine myeloid cells produce excessive quantities of TNF-α and IL-1β (12), it is possible that the increased bone resorption activity of monocytes from AD-HIES patients (75) resulted from increased production of these cytokines. Osteoclasts arise from the myeloid lineage, and the findings with

human monocytes are consistent with increased osteoclastogenesis and/or osteoporosis in mice lacking STAT3 in hematopoietic cells (77) or osteoblasts (78). This suggests that reduced STAT3 activity in osteoclasts and osteoblasts contributes to osteoporosis and susceptibility to bone fractures in AD-HIES. The STAT3-activating cytokine(s) responsible for attenuating osteoclastogenesis under physiological conditions remain to be identified; however the IL-6 family is probably central to this process as evidenced by increased development of osteoclasts in gp130-deficient mice (79) and STAT3-dependent, IL-6-mediated inhibition of in vitro generation of osteoclasts from murine bone marrow progenitors and human monocytes (80) (Table II). Craniosynostosis represents a specific bone abnormality that can arise from haploinsufficiency of *TWIST1* (81). Interestingly, STAT3 binds to the TWIST promoter and induces transcription, whereas STAT3 inhibition reduces TWIST expression (82). Thus, it is likely that compromised signaling via the STAT3/TWIST axis explains craniosynostosis in AD-HIES.

Hyper-IgE production. The most intriguing aspect of HIES remains the "hyper-IgE" component. Although it is possible to explain the deficits in Ag-specific humoral immunity in AD-HIES, it is difficult to understand the defect in immune regulation that manifests as dysregulated IgE production. However, several possible explanations have been excluded. First, hyper-IgE is not due to a B cell-intrinsic defect because B cells from AD-HIES patients do not spontaneously produce high amounts of IgE, at least not in vitro (83). Furthermore, because signaling through the IL-21R/STAT3 pathway is required for Blimp-1 expression (38, 71), impaired induction of Blimp-1 in AD-HIES is at odds with any form of hyperimmunoglobulinemia. Second, because IL-21 inhibits IgE production by murine B cells (19, 38), it was proposed that a lack of STAT3-dependent, IL-21-mediated signaling in human B cells contributed to elevated serum IgE levels in AD-HIES and (10, 48). However, this is unlikely because IL-21 actually induces IgE production by human B cells and synergizes with IL-4 to result in secretion of very high levels of IgE (83). An alternative explanation may lie in the observation that production by $CD4^+$ T cells of IL-10 and IFN-γ, which negatively regulate IgE production by human B cells (84), is reduced in AD-HIES (54–56, 83). The constraints on IgE production normally applied by IFN-γ and IL-10 would be minimized in AD-HIES not only by their reduced production, but also by the impaired ability of cells to respond to these cytokines because they can both activate STAT3 (11, 14). Although this is an attractive possibility and may contribute to the hyper-IgE phenotype (83), it is unlikely to be the sole explanation for the extreme magnitude of the IgE increase, because a complete deficiency in the Th1 lineage due to mutations in *IL-12Rβ1* and *IFN-γR* results in relatively modest increases in IgE (85). Instead, the magnitude of the IgE increase in AD-HIES suggests a feed-forward loop involving cooperation between multiple cell types, such as those of the immune system and the skin. Indeed, a role for nonhematopoietic cells in the dysregulated production of IgE is consistent with the finding that bone marrow transplantation failed to correct the hyper-IgE phenotype of classical AD-HIES (86).

To date, dysregulated IgE production has not been reported in STAT3-deficient mice. However, it may be reduced or within the normal range because, unlike humans (54–56, 83), production of IFN-γ by $CD4^+$ T cells from mice lacking STAT3 in immune cells is increased (12, 29). This, together with differences in the ability of IL-21 to regulate IgE secretion by human (83) and murine (19, 38) B cells, may limit existing animal models of STAT3 deficiency in elucidating the exact mechanism underlying production of extremely high levels of IgE in AD-HIES. However, important clues may come from analysis of other human monogenic disorders that result in hyper-IgE levels (84). Interestingly, several of these conditions are associated with intrinsic defects in keratinocyte function (e.g., ichthyosis vulgaris (mutations in *Filaggrin*) and Netherton syndrome (mutations in *SPINK5*) (84)), further supporting a causal relationship between immune cells, skin cells, and aberrant IgE production. This is clearly an important aspect of HIES that warrants detailed investigation, the outcomes of which may reveal strategies to attenuate IgE production in numerous pathologies (84).

STAT3-deficiency in humans vs mice

Although the deficit in Th17 cells plus defects in the production of Ag-specific Ab, bone development, and keratinocyte biology are shared by AD-HIES patients and conditional STAT3-deficient mice, the HIES phenotype was not predicted by STAT3-deficient mice. This may be due to a requirement for the loss of STAT3 from multiple cell lineages for the various clinical manifestations of AD-HIES, a scenario not yet tested in mice. Alternatively, it may reflect differences between human and murine immune systems, such as differences in IFN-γ production by STAT3-deficient human (decreased) (54–56) and murine (increased) (12, 29) $CD4^+$ T cells. This may explain the overt autoimmunity that develops in myeloid-specific STAT3-deficient mice (11, 12) but does not phenocopy in AD-HIES (48). Similarly, it remains to be determined whether DC development is impaired in AD-HIES as reported for STAT3-deficient mice (13). Another explanation for differences between STAT3-deficient mice and humans is that the low level of functional STAT3 in patients with AD-HIES may be sufficient for some basal cellular responses, which are completely abrogated in STAT3-null lineages. Although germline STAT3 deficiency is embryonically lethal (17) and lineage-specific deletion of STAT3 restricts functional analysis of STAT3 to defined cell types, a more appropriate animal model of AD-HIES may lie in the generation of knock-in mice expressing a common mutation in one allele of STAT3.

Conclusions

Over the past four decades, great progress has been made in defining the clinical aspects of AD-HIES, with the last 12 mo seeing the discovery of the genetic lesion causing this disease. This has led to our understanding of the immunological defect underlying infection susceptibility, highlighted critical roles for STAT3 in specific cell types and cytokine signaling in antimicrobial and epithelial immunity, and reminded us of the power of "experiments of nature" in dissecting complex biological systems. Continued investigation into the consequences of STAT3-deficiency in human cell lineages will reveal additional roles for STAT3 in numerous biological processes. Such studies will hopefully illuminate the molecular mechanisms responsible for many other aspects of AD-HIES, especially the hyper-IgE component, as well as the genetic lesion causing AR-HIES, and result in improved therapies for patients with these disorders.

Disclosures

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