

Clinical reviews in allergy and immunology

Series editors: Donald Y. M. Leung, MD, PhD, and Dennis K. Ledford, MD

T_H17 deficiency in human disease

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The differentiation of naive T cells into distinct subsets of effector T cells is critical for effective immunity against a wide variety of infectious agents in the environment. Activation of innate immune responses by *Candida* species through pattern-recognition receptors directs the subsequent development of naive T cells into T_H17 cells, which are essential for effective mucosal immunity against fungi. Thorough analyses of cohorts of patients with unusual susceptibility to chronic mucocutaneous candidiasis resulting from T_H17 deficiency have confirmed the role of T_H17 cells and T_H17 cytokines in human host defense against *Candida* species and have provided valuable insights into the complex process of T_H17 cell development. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: *T_H cells, Candida species, fungi, T_H17 cell, pathogen-recognition receptors, cytokines, transcription factors, differentiation, chronic mucocutaneous candidiasis*

Effective host defense against a wide variety of pathogens in our environment requires well-coordinated innate and adaptive immune responses. The innate immune system detects the presence of invading pathogens through widely expressed pathogen-recognition receptors (ie, Toll-like receptors [TLRs], nucleotide oligomerization domain–like receptors, retinoic acid-inducible gene I [RIG-I]–like receptors, and C-type lectins), leading to the subsequent activation of an adaptive immune response that destroys pathogens incompletely eliminated by the innate immune system (reviewed in Kawai and Akira¹). The innate immune system is germline encoded and characterized by limited diversity against invariant pathogen-associated molecular patterns, whereas adaptive immune responses are characterized by much greater diversity and specificity resulting from somatic recombination. The development and regulation of distinct subsets of T_H cells is essential for protection against a wide range of pathogens (ie, extracellular vs intracellular).

T_H cells are T cells that provide help or activating signals to other immune cells through the production of cytokines. The first characterization of T_H1 and T_H2 cell subsets occurred over 2

Abbreviations used

AD:	Autosomal dominant
AIRE:	Autoimmune regulator
APECED:	Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
APS-1:	Autoimmune polyendocrine syndrome 1
AR:	Autosomal recessive
CMC:	Chronic mucocutaneous candidiasis
DOCK8:	Dedicator of cytokinesis 8
HIES:	Hyper-IgE syndrome
IL-17R:	IL-17 receptor
IRAK-4:	IL-1 receptor–associated kinase 4
Mincle:	Macrophage-inducible C-type lectin
MyD88:	Myeloid differentiation factor 88
NK:	Natural killer
ROR:	Retinoic acid–related orphan receptor
STAT:	Signal transducer and activator of transcription
TLR:	Toll-like receptor
Treg:	Regulatory T

decades ago and was based on the profile of cytokines secreted by each subset.² T_H1 cells are characterized by production of IFN- γ , are required for defense against intracellular pathogens, and mediate delayed-type hypersensitivity. IFN- γ enhances the bactericidal activities of macrophages, upregulates MHC class I and class II expression, and promotes production of opsonizing antibodies by B cells. T_H2 cells are characterized by production of IL-4, IL-5, and IL-13 and are involved in defense against parasitic infections, mediate production of IgE, and promote eosinophilic inflammation.³ The production of IL-4 supports the production of neutralizing antibodies against extracellular bacteria that characterize humoral immunity.

Subsequent analysis of T-cell differentiation has revealed far greater complexity in the T_H cell subsets that can be generated. These T_H cells are defined by their expression of specific transcription factors and functions. For instance, regulatory T (Treg) cells are characterized by expression of forkhead box protein 3 and are critical for the maintenance of self-tolerance. However, there is plasticity in T-cell differentiation because Treg cells can be induced to lose forkhead box protein 3 expression and adopt a T_H1 cell phenotype capable of IFN- γ production and autoimmune destruction.⁴ More recently, an additional subset of effector T cells, the T_H17 subset, has been identified.⁵ The development of T_H17 cells is dependent on exposure of naive T cells to a complex milieu of cytokines that leads to the expression of a unique set of transcription factors required for T_H17 differentiation (described below). Similar to Treg cells, the plasticity of T_H17 cells has been observed in lymphopenic environments in murine models in which T_H17 cells can convert into

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D.R.M. is supported by National Institutes of Health grant 5K08AI76625.

Disclosure of potential conflict of interest: D. R. McDonald declares that he has no relevant conflicts of interest.

Received for publication January 10, 2012; revised March 16, 2012; accepted for publication March 26, 2012.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2012.03.034

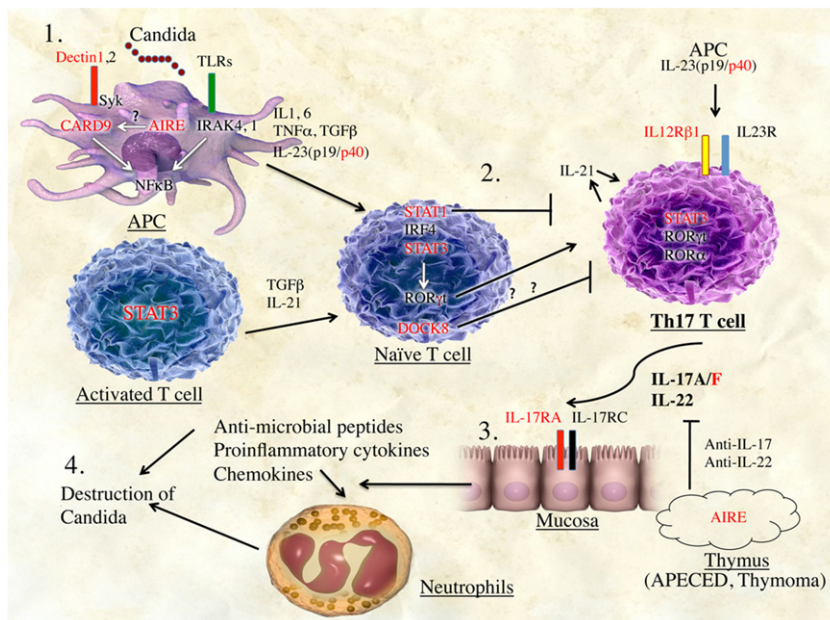


FIG 1. Summary of T_H17 development and human diseases that impair T_H17 development or function. **1**, IL-1 β , IL-6, IL-23, TNF- α , and TGF- β are secreted after activation of antigen-presenting cells (APC) by fungal cell-wall components. Additionally, activated T cells produce TGF- β and IL-21. **2**, Exposure of naïve T cells to this cytokine milieu induces their differentiation into T_H17 cells. Gain-of-function mutations in patients with *STAT1* as well as *STAT3* functional deficiency and *DOCK8* deficiency block T_H17 differentiation. **3**, T_H17 cells produce IL-17A/F and IL-22, which induces production of proinflammatory cytokines, chemokines, and antimicrobial peptides by mucosal cells, leading to recruitment of neutrophils to sites of infection and destruction of *Candida* species (**4**). Genes in red represent currently known mutations that impair T_H17 cell development or T_H17 effector functions, as described in the text.

IFN- γ -secreting T_H1 cells.⁶ Thus characterization of the cytokines, signaling pathways, and transcription factors that direct T-cell differentiation is critical for understanding T-cell differentiation and function. Identification of novel mutations in genes that impair T-cell differentiation and function in immune-deficient patients will expand our knowledge of the role of specific T-cell subsets in host defense against pathogens.

Both murine models and analysis of T_H17 cells in human subjects have demonstrated that T_H17 cells play a critical role in mucosal immunity.^{7,8} The recent descriptions of infectious susceptibility to chronic mucocutaneous candidiasis (CMC) in patients with defects in T_H17 development and function resulting from single-gene mutations or as part of a syndrome have served to clearly define the role of T_H17 cells in human host defense. The complex processes of T_H17 cell development have been previously described in this issue and elsewhere^{7,9} and will only be mentioned below in relation to other immunodeficiency diseases that affect T_H17 cell development and function. Knowledge of the mechanisms of T_H17 cell differentiation and inborn errors of T_H17 cell function in patients has expanded rapidly over the past several years. This review will summarize the clinical aspects of patients with genetic defects that result in T_H17 deficiency.

THE IL-17 CYTOKINE FAMILY

The IL-17 cytokine family consists of 6 members (IL-17A through IL-17F). Among IL-17 family members, IL-17A and IL-17F share the highest amino acid sequence homology (50%).¹⁰ The receptors for IL-17 include a family of 5 receptors (IL-17RA through IL-17RE). Heterodimers of IL-17RA and IL-17RC

constitute the receptors for IL-17A and IL-17F. IL-17A and IL-17F are preferentially produced by T_H17 cells (along with IL-21 and IL-22). IL-17A and IL-17F form homodimers and heterodimers and induce the expression of proinflammatory cytokines (IL-1, IL-6, TNF- α , granulocyte colony-stimulating factor, and GM-CSF), chemokines (CXCL1, CXCL5, IL-8, CCL2, and CCL7), antimicrobial peptides (defensins and S100), and matrix metalloproteinases (MMP1, MMP3, and MMP13) from the endothelium, epithelia, and fibroblasts.⁹ As a result, T_H17 cells can promote granulopoiesis and recruitment of neutrophils to sites of infection and provide host defense against extracellular bacteria and fungi. Interestingly, a variety of other T-cell types, including CD8⁺ T cells (T_C17), $\gamma\delta$ T cells ($\gamma\delta$ -17), and natural killer (NK) T cells (NKT-17), can produce IL-17A and IL-17F (reviewed in Cua and Tato¹¹). Furthermore, innate immune cells, including neutrophils, monocytes, NK cells, and lymphoid tissue inducer-like cells, can produce IL-17A and IL-17F. Finally, IL-17A has been shown to be produced by intestinal Paneth cells,¹² whereas colonic epithelial cells have been shown to express *IL17F* mRNA, suggesting that a variety of cell types can play roles in host defense against fungi and extracellular bacteria.⁸ Less is known about the regulation of IL-17 from these cell types.

DEVELOPMENT OF T_H17 CELLS

The differentiation of naïve T cells into T_H17 cells is a highly complex process and is incompletely understood. T_H17 cell development is directed by multiple cytokines, including IL-1 β , IL-6, TGF- β , IL-21, and IL-23 (Fig 1), which leads to

TABLE I. Conditions that impair T_H17 development

Condition	Phenotype	Genotype
T _H 17 deficiency within a syndrome		
AD-HIES	Increased IgE level, <i>S aureus</i> abscesses, pneumonia, pneumatocele formation, candidiasis	<i>STAT3</i> mutations
AR-HIES	Increased IgE level, eosinophilia, atopy, recurrent sinopulmonary infections, herpesvirus, candidiasis	<i>DOCK8</i> mutations
GOF-STAT1	Pneumonia, <i>P jirovecii</i> pneumonia, cytomegalovirus, autoimmunity, cancers, candidiasis	<i>STAT1</i> mutations within exon 10
APS-1/APECED	Autoimmune polyendocrinopathy, ectodermal dystrophy, candidiasis	<i>AIRE</i> mutations
Thymoma	Autoimmunity, myasthenia gravis, rarely candidiasis	Absent <i>AIRE</i> expression in tumor
Pure T _H 17 deficiency		
IL-17R	Candidal dermatitis, <i>S aureus</i>	<i>IL17RA</i> and <i>IL17F</i> mutations
IL-17 ligand	dermatitis	

activation of the transcription factors signal transducer and activator of transcription (STAT) 3 and interferon regulatory factor 4 and subsequent expression of retinoic acid–related orphan receptor (ROR) γ t.^{7,13–17} These cytokines are produced by activated T cells and antigen-presenting cells stimulated through pathogen-recognition receptors (ie, Dectin-1/2, TLR2, TLR4, and macrophage-inducible C-type lectin [Mincle]) in response to pathogen-associated molecular patterns (β -glucans, lipoproteins, peptidoglycan, and zymosan) found within the cell walls of fungi and bacteria.¹⁸ Several other transcription factors, including ROR α , basic leucine zipper transcription factor (Batf), Runt-related transcription factor 1 (Runx1), and I κ B ζ can cooperate with ROR γ t to regulate T_H17 differentiation (reviewed in Iwakura et al⁹). Additionally, the transcription factors SMAD-3 and activating transcription factor 2 (ATF-2) are required for expression of IL-23p19, which promotes T_H17 differentiation.¹⁹

Insights into the cytokine milieu required for T_H17 development in human subjects have been gained from the study of patients with defects in these cytokine pathways. Myeloid differentiation factor 88 gene (*MyD88*) and IL-1 receptor–associated kinase 4 (*IRAK-4*) are essential effectors of the IL-1 receptor and TLR signaling pathways. Studies by de Beaucoeur et al²⁰ demonstrated that T_H17 T-cell populations are intact in patients with *IRAK-4* and *MyD88* deficiency, who are unable to respond to IL-1 β . This observation suggests that although IL-1 β might promote T_H17 differentiation, it is not absolutely required. Because all TLR signaling (with the exception of TLR3) is also blocked in these patients, TLR-induced IL-6 production is absent.²¹ The lack of IL-1 responsiveness and impaired IL-6 production in *MyD88*- and *IRAK-4*-deficient patients is manifested clinically by reduced fever and reduced acute-phase reactant production in these patients during invasive bacterial infections. Given that IL-6 plays a critical role in T_H17 development, it is

clear that IL-6 induced by the stimulation of other pathogen-recognition receptors is adequate for T_H17 cell development. Other functional sources of IL-6 in *MyD88*- and *IRAK-4*-deficient patients include activation of TLR3, nucleotide oligomerization domain–like receptors, RIG-I–like receptors, and C-type lectins.

In contrast, IL-12p40– and IL-12R β 1–deficient patients, both of whom have impaired IL-23 signaling, have reduced populations of T_H17 cells.²⁰ IL-12p40 and IL-23p19 form heterodimers to make active IL-23, whereas IL-12R β 1 and IL-23R heterodimerize to form the active IL-23 receptor. The reduction in T_H17 populations in IL-12p40– and IL-12R β 1–deficient patients is not as severe as in *STAT3*-deficient patients, suggesting that IL-23 is important for T_H17 development, maintenance, or both, but some redundancy might exist to allow reduced T_H17 development. Because candidal infections in IL-12p40– and IL-12R β 1–deficient patients are not common, it is likely that the majority of these patients retain adequate T_H17 function to prevent susceptibility to CMC.²⁰ Additionally, IL-12 has been shown to play a role in anti-candidal immunity. Because the IL-12p40– and IL-12R β 1–deficient patients are obviously deficient in IL-12 responses, which accounts for their susceptibility to mycobacterial infections, identification of IL-23R– or IL-23p19–deficient patients would likely provide more specific insight into the importance of IL-23 in human T_H17 differentiation and host defense against *Candida* species.

CMC DISEASE AS PART OF A SYNDROME

Candida albicans is a commensal organism that can cause transient mucocutaneous infections of the skin, nails, and oral and genital mucosae in healthy subjects. In immunocompromised subjects, however, *C albicans* can cause chronic mucocutaneous and sometimes fatal invasive infections. Neutrophil defects are associated with systemic candidiasis and susceptibility to a wide variety of bacteria. CMC disease and invasive candidiasis have also been described in a large Iranian family with a homozygous nonsense mutation in caspase recruitment domain–containing protein 9 (*CARD9*),²² a signaling protein that, along with spleen tyrosine kinase (*Syk*), is downstream of the antifungal receptors Dectin-1, Dectin-2, and Mincle (Fig 1). Severe T-cell deficiencies, such as severe combined immunodeficiencies and HIV, are associated with CMC disease, but they also are associated with other bacterial, viral, and opportunistic infections. Infectious susceptibility that is primarily limited to patients with CMC represents a unique subset of immune deficiency.

To date, several complex human diseases have been identified that impair T_H17 cell differentiation and can result in susceptibility to CMC disease as one manifestation of a more complex syndrome (Table I). These include autosomal dominant (AD) hyper-IgE syndrome (HIES) with mutations in *STAT3*²³ and autosomal recessive (AR) HIES with mutations in the dedicator of cytokinesis 8 gene (*DOCK8*).²⁴ Furthermore, autoimmune polyendocrine syndrome 1 (APS-1), which is also known as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), and some cases of thymoma also result in susceptibility to CMC through impairment of T_H17 functions.²⁵ These secondary causes of T_H17 function have provided useful insights into the mechanisms that regulate human T_H17 effector development and function and serve to confirm the essential role of T_H17 cells in mucosal immunity against *Candida* species.

AD-HIES caused by mutations in *STAT3*

AD-HIES caused by mutations in *STAT3* is a multisystem immune deficiency characterized by highly increased serum levels of IgE, local and invasive infections with *Staphylococcus aureus* that result in cold abscesses and recurrent pneumonia with pneumatocele formation, skeletal abnormalities, and coarse facial features.²⁶⁻²⁸ Additionally, development of CMC is a common complication in these patients. The cytokines IL-6 and IL-21, which activate *STAT3*, play significant roles in the development of human T_H17 T cells,²⁹ as discussed above. As previously mentioned, *STAT3* activation induces the expression of ROR γ t, a transcription factor required for the development of T_H17 T cells and the subsequent expression of IL-17, IL-21, IL-22, and IL-23 receptor, which play essential roles in T_H17 function. Because patients with AD-HIES caused by *STAT3* mutations are susceptible to CMC disease, *STAT3* is essential for T_H17 cell development, and T_H17 cells play an important role in mucosal immunity against *Candida* species. Ma et al²³ evaluated these patients for potential defects in T_H17 development. Analysis of T-cell blasts generated from total CD4⁺ T cells of patients with AD-HIES revealed significant reductions in IL-17⁺ T-cell numbers, and subsequent stimulation of these CD4⁺ T cells resulted in no production of IL-17. Furthermore, production of IL-22, a T_H17-derived cytokine involved in epithelial and mucosal immunity, was absent from CD4⁺ T cells of patients with AD-HIES. Consistent with the essential role of *STAT3* in ROR γ t expression, upregulation of ROR γ t expression was reduced in stimulated CD4⁺ T cells of patients with AD-HIES compared with those of healthy control subjects. Furthermore, sorted naive CD4⁺ T cells of patients with AD-HIES did not differentiate into T_H17 T cells when stimulated with anti-CD2 and anti-CD3 plus anti-CD28 in the presence of IL-1 β plus IL-6 or IL-23, confirming the requirement for *STAT3* in T_H17 differentiation. Consistent with these observations, Milner et al³⁰ found that blood cells obtained from patients with AD-HIES that were stimulated overnight with *S aureus* or *Candida* species did not generate memory CD4⁺IL-17⁺ T cells. Thus analysis of T cells from patients with *STAT3* mutations has clearly demonstrated an essential role for *STAT3* in T_H17 differentiation and mucosal and epithelial immunity against *Candida* species and *S aureus* (Fig 1).^{23,30,31} As mentioned above, T_C17, $\gamma\delta$ -17, and NKT-17 cells are also sources of T_H17 cytokines¹¹; however, they either do not produce T_H17 cytokines or they produce inadequate quantities of T_H17 cytokines in patients with AD-HIES to prevent CMC disease. This suggests that *STAT3* is likely to be involved in T_H17 cytokine production in T_C17 cells, $\gamma\delta$ -17 cells, and NKT-17 cells.

DOCK8

AR-HIES caused by mutations in *DOCK8* is characterized by highly increased serum IgE levels, hypereosinophilia, recurrent sinopulmonary infections, unusual susceptibility to herpesvirus infections, candidal dermatitis, and atopy.³²⁻³⁴ In addition, *DOCK8*-deficient patients tend to be T-cell lymphopenic, with poor T-cell proliferation after activation with anti-CD3 and anti-CD28. The molecular basis of cutaneous candidal infections in these patients is incompletely understood at present. Previous analysis of a cohort of patients with AR-HIES, some of whom were later confirmed to have *DOCK8* deficiency, revealed that these patients have defects in T_H17 differentiation.²⁴ ROR γ t expression, which is critical for T_H17 differentiation, was markedly

reduced in peripheral T cells from patients with AD-HIES caused by *STAT3* mutations, as well as in patients with AR-HIES. Interestingly, *in vitro* induction of ROR γ t expression by naive T cells was intact in the patients with AR-HIES but not in the patients with AD-HIES. These data suggest that the initial steps of T_H17 differentiation are intact in the patients with AR-HIES but that subsequent steps of differentiation are impaired (Fig 1). IL-17 production was impaired in both groups of patients with HIES, although the impairment was more severe in the patients with *STAT3* mutations. Thus defective T_H17 differentiation occurs through a different mechanism in patients with AR-HIES versus patients with AD-HIES caused by *STAT3* mutations. It is likely that impaired T_H17 differentiation and IL-17 production contribute to the susceptibility of patients with AR-HIES with *DOCK8* mutations to candidal dermatitis. It is also possible that a more global impairment in T-cell function in *DOCK8*-deficient patients, as demonstrated clinically by their susceptibility to viral infections, also contributes to candidal infections. A clearer understanding of the cause or causes of impaired T_H17 differentiation in *DOCK8*-deficient patients might help to further elucidate the complex process of T_H17 differentiation.

Gain-of-function mutations in *STAT1*

In a search for genetic causes of AD-CMC disease, 2 groups of investigators independently identified heterozygous mutations in *STAT1* as a novel cause of deficiency of T_H17 differentiation and AD-CMC. In one study van de Veerdonk et al³⁵ analyzed 5 families with severe CMC disease. Other documented infections included pneumonia and one case of *Pneumocystis jirovecii* pneumonia with cytomegalovirus infection. Additionally, several patients had autoimmune disease (autoimmune hepatitis, autoimmune hemolysis, or hypothyroidism), and a few had cancers (esophageal cancer or squamous cell carcinoma). Functional analysis of blood cells revealed defects in *Candida* species-stimulated production of IFN- γ , IL-17, and IL-22. Further functional analyses demonstrated defective functioning of IL-12 and IL-23 signaling pathways. These studies were followed by array-based sequence capture and next-generation sequencing of 100 candidates genes relevant to IL-12 and IL-23 signaling and T_H1 and T_H17 responses. This analysis identified heterozygous mutations within highly conserved residues in exon 10 of *STAT1*, which lies within the coiled-coil domain.

Simultaneously, Liu et al³⁶ analyzed additional genetic causes of CMC disease by applying a genome-wide strategy based on whole-exome sequencing. All patients had CMC disease, and several of these patients had autoimmune disorders (thyroid autoimmunity or systemic lupus erythematosus), cerebral aneurysms, or squamous cell carcinoma. Candidate variations were selected by filtering out known polymorphisms obtained from several databases. This analysis identified heterozygous variations in the *STAT1* gene all within the coiled-coil domain. Functional analysis of one of the *STAT1* mutant alleles (*STAT1* R274Q) revealed enhanced activation of a γ -activated sequence reporter construct in response to IFN- α , IFN- γ , and IL-27. The increased transcriptional activation by the *STAT1* R274Q allele was associated with impaired nuclear dephosphorylation. Thus *STAT1* mutations within the coiled-coil domain appeared to be gain-of-function mutations. Stimulation of EBV-immortalized B cells and fibroblasts from patients with gain-of-function mutations in *STAT1* resulted in augmented responses to IFN- α , IFN- γ , and IL-27,

cytokines known to be antagonistic to T_H17 development.^{37,38} Interestingly, cellular responses to predominantly STAT3-activating cytokines that promote T_H17 differentiation, such as IL-6 and IL-21, also resulted in increased STAT1 phosphorylation in EBV B cells from patients with gain-of-function *STAT1* mutations compared with that seen in healthy control subjects. The enhanced STAT1 activation might be significant because STAT1 activation has been shown to be antagonistic to T_H17 development (Fig 1).¹³ Finally, percentages of IL-17A⁺, IL-17F⁺, and IL-22⁺ T cells, as well as production of IL-17A and IL-22 in patients with gain-of-function *STAT1* mutations, were significantly lower than those of healthy control subjects and patients with loss-of-function *STAT1* mutations, providing the molecular basis for CMC disease in these patients. Interestingly, enhanced cellular responses to type 1 interferon in these patients might underlie a predisposition to autoimmune disorders observed in several of these patients because autoimmune disorders have been associated with an increased type 1 interferon signature.^{39,40} A fascinating aspect of the role of *STAT1* in human immune deficiencies is that mutations in 1 gene can lead to 3 very different phenotypes: CMC disease,³⁶ mycobacterial disease,⁴¹ or susceptibility to viral disease.⁴²

APS-1/APECED and thymoma

The syndrome of APS-1, or APECED, is the result of AR mutations in the autoimmune regulator gene (*AIRE*).⁴³ *AIRE* is a transcription factor expressed by medullary thymic epithelial cells, which is responsible for the expression of a wide variety of tissue-specific antigens within the thymus. Expression of these tissue-specific antigens in the thymus leads to deletion of self-tolerance in T cells maturing within the thymus. However, the lack of functional *AIRE* in patients with APECED results in impaired central T-cell tolerance, leading to the generation of autoantibodies. The clinical presentation of APECED is variable, but the majority of patients have CMC disease, hypoparathyroidism, and Addison disease.²⁵ CMC is the sole immune deficiency in patients with APECED and is one of the earliest manifestations of the syndrome. Neutralizing antibodies against cytokines, in particular type 1 interferons and T_H17 cytokines, are the most prevalent autoantibodies in patients with APECED (reviewed in Kisand et al²⁵). This high prevalence of autoantibodies against type 1 interferons and IL-22 is virtually diagnostic for APECED. Autoantibodies against IL-17A, IL-17F, and IL-22 appear to be more prevalent in patients with APECED with CMC than those without CMC, suggesting a causal role in CMC (Fig 1). Kisand et al⁴⁴ also observed that IL-17 and IL-22 production was markedly decreased from *Candida* species-stimulated blood cells derived from patients with APECED with CMC disease, perhaps because of autoimmune destruction of IL-17⁺ and IL-22⁺ T cells. Interestingly, Pedroza et al⁴⁵ observed that the *AIRE* protein can also function as a signaling effector downstream of Dectin-1 in blood cells and a monocytic cell line (Fig 1). These observations suggest that *AIRE* mutations in patients with APECED might contribute to impaired innate responses to *Candida* species, which could subsequently impair IL-17 and IL-22 production, although this remains to be formally evaluated.

Thymomas are tumors that originate from thymic epithelial cells. The majority of these tumors did not express *AIRE* (Fig 1). Thymomas are associated with autoimmune manifestations, most notably with antibodies against muscle acetylcholine receptors that cause myasthenia gravis. Autoantibodies against type

1 interferons are also common in patients with thymomas; however, autoantibodies against T_H17 cytokines are rare.⁴⁴ As a result, CMC is only rarely associated with thymoma. For unknown reasons, patients with APECED and thymomas, despite having high titers of neutralizing antibodies against IFN- α and IFN- ω , do not have increased susceptibility to viral infections. Possible explanations are that IFN- β and IFN- λ might compensate or local concentrations of type 1 interferons might be adequate to activate biological responses. The rare occurrence of CMC disease in patients with thymomas with anti-IL-17 cytokine antibodies provides additional circumstantial evidence of the importance of IL-17 cytokines in CMC disease.

INBORN ERRORS OF IMMUNITY RESULTING IN PURE CMC DISEASE

Recently, 2 genetic causes of pure CMC disease have been identified in human subjects (Table I). Puel et al⁴⁶ studied subjects and families with infectious susceptibility limited to CMC for inborn errors of IL-17, IL-17R, and IL-22. Other known causes of CMC disease were excluded clinically and genetically. Evaluation of an infant who was the product of a consanguineous union and presented with candidal dermatitis and subsequent *S aureus*-induced dermatitis resulted in the first description of AR-CMC disease caused by a homozygous nonsense mutation in the *IL17RA* gene (Q248X/Q248X). The Q248X/Q248X mutation resulted in absent expression of IL-17RA on the patient's blood cells and fibroblasts and a complete absence of responsiveness to IL-17A/IL-17F. Responsiveness to IL-17 cytokines was restored to the patient's fibroblasts by means of transfection with wild-type IL-17RA, confirming the lack of IL-17RA expression as the cause of the patient's CMC disease.

Additionally, Puel et al⁴⁶ evaluated a multiplex family with AD inheritance of CMC disease, identifying a heterozygous missense mutation in the *IL17F* gene. The mutation resulted in the substitution of the serine residue at position 65 of the protein with a leucine residue (S65L). The S65 residue is conserved across all mammalian species and is believed to be involved in ligand receptor interaction. The production of inflammatory cytokines by normal fibroblasts and blood cells elicited by mutant *IL17F*(S65L) homodimers was severely impaired. In addition, stimulation of normal fibroblasts and keratinocytes with heterodimers consisting of *IL17F*(S65L)/*IL17FWT* or *IL17F*(S65L)/*IL17A* resulted in severely impaired production of inflammatory cytokines, demonstrating a dominant negative effect of *IL17F*(S65L). Interestingly, the *IL17F*(S65L) mutation was also found in 2 apparently healthy members of the family, suggesting incomplete clinical penetrance. At present, although experience is very limited with patients having genetic defects in *IL17F* or *IL17RA*, these observations support a role for T_H17 cells and T_H17 cytokines that is limited to mucosal immunity against *Candida* species and possibly *S aureus* (Fig 1).

CONCLUSION

The study of multiple cohorts of patients with T_H17 deficiency that result from unique genetic defects has been invaluable in defining the role T_H17 cells and T_H17 cytokines in human mucosal host defense against *Candida* species and possibly *S aureus*. Many of these disorders cause susceptibility to more than 1 pathogen, including *Candida* species. In the cases of *STAT1*, *STAT3*,

IL12RB1, *DOCK8*, *IL17RA*, and *IL17F* mutations, thorough analyses of the molecular mechanisms that underlie these disorders have revealed defective T_H17 cell development or effector function that results in susceptibility to CMC disease. Some of these disorders have associated autoimmunity. Interestingly, CMC disease is a sequela of APS-1 and, rarely, of thymoma, as a result of neutralizing autoantibodies against IL-17 and IL-22. Of course, the common link among all these disorders is a deficiency in T_H17 effector function. CMC disease in T_H17 -deficient patients is likely caused by the lack of IL-17–induced production of antimicrobial peptides by mucosal cells and impaired recruitment of neutrophils that clear the *Candida* species. Analysis of T_H17 cell populations in MyD88- and IRAK-4-deficient patients was worthwhile because although they do not have CMC disease, the finding of normal T_H17 cell populations in these patients demonstrated that IL-1 β is not absolutely required for T_H17 cell development in human subjects. In rare cases oral candidiasis has been observed in patients with mutations in nuclear factor κ B essential modifier/IKK γ , who have reduced nuclear factor κ B activation.⁴⁷ T_H17 cell development is severely impaired in c-Rel^{-/-} mice, suggesting a role for nuclear factor κ B in T_H17 development.⁴⁸ Further analysis of patients with unusual susceptibility to CMC disease is likely to provide additional insights into the regulation of T_H17 cell development and function.

What is known?

- T_H17 T cells and T_H17 cytokines mediate mucosal immunity against fungi and, perhaps, *S aureus* in human subjects.
- T_H17 cells appear to be redundant for most other forms of immunity.
- Although IL-1 β promotes T_H17 development in murine models, it is not absolutely required for T_H17 development in human subjects.
- Analysis of *STAT1* mutations reveals great phenotypic variation: CMC disease, mycobacterial disease, or viral disease.
- STAT3 is a critical mediator of T_H17 T-cell development and resistance to CMC disease.

What is still unknown?

- Will T_H17 cytokines have therapeutic use in select cases of severe CMC disease?
- Could use of T_H17 cytokines clinically result in autoimmunity?
- What is the contribution of T_C17 cells, $\gamma\delta$ -17 cells, NKT-17 cells, neutrophils, monocytes, and lymphoid tissue inducer–like cells to mucosal immunity?
- What is the mechanism of impaired T_H17 development and candidiasis in *DOCK8*-deficient patients?
- Will analysis of additional patients and families with CMC disease identify novel genes important for T_H17 development?
- Will analysis of additional patients and families with CMC disease help to clarify the process of T_H17 development in human subjects?

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