

New host defense mechanisms against *Candida* species clarify the basis of clinical phenotypes

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Chronic *Candida* species infection of the skin and mucosal membranes is viewed as a group of disorders all sharing a similar clinical condition, the susceptibility to localized fungal infections, which can be isolated or as a feature associated with various other entities. Although the pathogenesis underlying such a tendency had previously been poorly understood, the last decade has witnessed significant progress in revealing the molecular and immunologic mechanisms involved in antifungal immunity. T_H17 cells and their specific cytokines (IL-17A and IL-17F cytokines and IL-22) are the main players in conferring antifungal protection. Autoimmune polyendocrinopathy and ectodermal dystrophy and hyper-IgE syndrome are 2 entities caused by different genetic mutations affecting distinct immune pathways but eventually share a similar clinical phenotype of *Candida* species infection. Impaired T_H17 responses, although mediated by different mechanisms, seem to underlie this common feature: neutralizing autoantibodies against IL-17A and IL-22 are involved in patients with autoimmune polyendocrinopathy and ectodermal dystrophy syndrome, whereas abnormal T_H17 proliferation and IL-17 production are observed in the latter. Although various degrees of T_H17 dysfunction were also observed in most cases of isolated chronic mucocutaneous candidiasis, only in very few families was a distinct mutation detected (caspase recruitment domain family, member 9 [CARD9]), thus indicating certain forms of chronic mucocutaneous candidiasis as monogenic with a Mendelian pattern of inheritance. Hopefully, these data will open the way for further searches for other genes and for introducing new treatment modalities. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Chronic mucocutaneous candidiasis, T_H17 cells, IL-17, IL-22

Candida albicans is a dimorphic fungus that can cause a variety of distinct disease forms in human subjects. Normally, this fungus is a commensal organism found in the gastrointestinal and

Abbreviations used

APECED: Autoimmune polyendocrinopathy and ectodermal dystrophy
CARD9: Caspase recruitment domain family, member 9
CMC: Chronic mucocutaneous candidiasis
HIES: Hyper-IgE syndrome
ROR: Retinoic acid–related orphan receptor
STAT3: Signal transducer and activator of transcription 3
Syk: Spleen tyrosine kinase
TLR: Toll-like receptor
Treg: Regulatory T

reproductive mucosa. However, in immunocompromised patients *C albicans* might be responsible for multiple disease states, either systemic or mucosal.

Systemic candidiasis usually presents as an acute, disseminated, and invasive form mainly in patients with both inherited and acquired neutrophil disorders or in patients with insertion of central lines. More commonly, *C albicans* can cause a mucosal and epidermal form of infection, typically presenting with chronic manifestations and thus called chronic mucocutaneous candidiasis (CMC).¹ CMC is now viewed as a collection of syndromes with the unifying feature of susceptibility to chronic or recurrent candidiasis localized to the skin, nails, and mucous membranes. The lesions, although not life-threatening, are disfiguring and debilitating, causing a major negative effect on quality of life. As a rule, there is essentially no predisposition to invasive disease, such as sepsis or pneumonia.

Because of the diversity of populations of patients with CMC, several clinical syndromes have been defined, differing in their clinical manifestations, severity, distribution, immunologic findings, and genetic features. Cutaneous *Candida* species infections are more frequently observed secondary to several clinical conditions, such as HIV, diabetes mellitus, intensive care conditions, neoplasia, long-term use of broad-spectrum antibiotics or immunosuppressive agents, and any global T-cell deficiency disorders, such as Di George syndrome or severe combined immunodeficiency.² All such conditions are characterized by general susceptibility to multiple other pathogens and various severe invasive infectious diseases.

In contrast to these entities, more rarely, CMC can be considered a primary condition, either as a prominent clinical feature of several identified primary immunodeficiency syndromes, such as hyper-IgE syndrome (HIES) and autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED), or as an isolated phenomenon with no other overt infection or autoimmune manifestation. These nonsyndromic cases of CMC, first described in 1967, can be sporadic, but

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multiplex families with both dominant and recessive inheritance have been described.³ Significant progress has been made regarding the molecular background and pathomechanics of primary CMC since the first published case on primary candidiasis by Thorpe and Handley⁴ about 8 decades ago. Various investigations conducted recently, both on animal models and in human subjects, have transitioned the description of such cases from idiopathic with an impaired cell-mediated immunity to *C albicans* to more well-established primary immunodeficiencies. These studies deciphered the specific cells, signal transduction pathways, cytokines, and genes involved.

Traditionally, the immune response against *Candida* species was thought to be mediated by CD4⁺ T_H1 lymphocytes and their major cytokine IFN- γ . Later, Farah et al⁵ reported that IFN- γ knockout mice were not susceptible to oral candidiasis. The development of murine models for CMC, the availability of numerous knockout and transgenic strains, and the introduction of the relatively newly described CD4⁺ effector T cells T_H17 cells and their related cytokines has facilitated the process of understanding the mucocutaneous immunity against *Candida* species.

In this report we will briefly summarize the pathways for *Candida* species sensing and signal transduction, T_H17 cell development, and their role in cutaneous antifungal immunity and give an overview on the molecular background underlying the several primary genetic disorders associated with susceptibility to peripheral *Candida* species.

CANDIDA SPECIES SENSING AND INNATE ANTIFUNGAL IMMUNITY

During an infection with *Candida* species, both the innate and adaptive arms of the immune system are involved in mounting a protective response. The first step is the recognition of the fungal pathogen by cell-surface receptors located on professional phagocytes and dendritic cells. Several pathogen-associated molecular patterns (eg, mannans, glucans, and chitin) are recognized by receptors grouped into several families, such as Toll-like receptors (TLRs), the C-type lectin receptors, and others.

The detailed *Candida* species-sensing pathways are beyond the scope of this review, but apparently some of the TLRs seem to be involved in host defense against *Candida* species. TLR2 and TLR4 are involved in the host interaction with *C albicans* and play a significant role in the development of host immune response during candidiasis.⁶ Recognition of *Candida* species by TLRs activates intracellular signaling pathways that might contribute to the polarization toward a proinflammatory T_H17 response.⁶ Furthermore, in a TLR2 knockout murine model increased dissemination of *Candida* species to the lymph nodes and spleen was observed with decreased neutrophil function.⁷

Still, the C-type lectin receptors, mainly Dectin-1 and Dectin-2, have been demonstrated to be pivotal in the immune response to *C albicans*.⁸ Dectin-1 recognizes pathogen-associated molecular patterns (β -glucan) and signals through immunoreceptor tyrosine-based activation motif, which becomes phosphorylated by sarcoma kinases. These signaling events are followed by the recruitment and activation of spleen tyrosine kinase (Syk). Dectin-1/Syk then engage caspase recruitment domain family, member 9 (CARD9), the intracellular signaling of which relays fungal recognition through the activation of nuclear factor κ B and mitogen-activated protein kinases.⁹ Dectin-1 seems to also

have a role in the innate immune response to fungal infections. For example, it was shown that it was a major initiator of the respiratory burst.⁸ On the other hand, Dectin-2 was shown to be the functional receptor for α -mannans, a known component of fungal structure.¹⁰ Dectin-2, which is expressed by dendritic cells, was recently shown to be essential in mediating protection against *Candida* species because survival was significantly decreased in Dectin-2-deficient mice when infected with *C albicans*. This defect was mainly due to the substantial reduction in cytokine production, especially those involved in T_H17 differentiation.¹⁰ The Dectin-Syk-CARD9-signaling pathway triggers the production of further cytokines, such as IL-1 β , TNF- α , IL-6, and IL-23, which are all contributing to antifungal immunity, including the generation of IL-17- and IL-22-producing T cells, so-called T_H17 cells (Fig 1).

T_H17 CELL DEVELOPMENT AND THEIR ROLE IN ANTIFUNGAL HOST DEFENSE

The T_H1 versus T_H2 model has dominated T-cell biology for many years. Yet the description of another T_H subset, the T_H17 lineage, about a decade ago has made a major shift in our understanding of the immune components conferring resistance to *Candida* species.¹¹ On activation by signaling through the T-cell receptor and costimulatory molecules, naive CD4⁺ T_H precursor cells can differentiate into 3 lineages of effector T_H cells (T_H1, T_H2, and T_H17 cells), depending on the local cytokine milieu. Each subset produces different cytokines that mediate distinct effectors mechanisms. T_H17 cells develop in the presence of IL-1 β , IL-6, and TGF- β . These cytokines act in a signal transducer and activator of transcription 3 (STAT3)-dependent manner to induce the expression of the retinoic acid-related orphan receptor (ROR) γ t, the lineage defining the transcription factor of T_H17 cells. In addition, they upregulate the expression of chemokine receptors CCR4 and CCR6, which is required for their migration to the skin and mucosa, respectively. IL-23 is important for T_H17 cell maintenance and expansion. Differentiated T_H17 cells secrete IL-17A and IL-17F, IL-21, IL-22, and IL-26 cytokines, which are known to promote cutaneous antifungal immunity by inducing the release of a wide range of proinflammatory danger signals, the expansion of antimicrobial factors, chemokine production at sites of infection, and recruitment of neutrophils.

Regulatory T (Treg) cells also play a role in the normal immune response to fungal infections. Treg cells can suppress T_H17 function and thus lead to reduced inflammatory responses against *Candida* species and avoidance of unnecessary inflammatory response.¹² Generation of induced Treg and T_H17 cells is reciprocally regulated. Depending on the concentration, TGF- β has the ability to induce both ROR γ t (important for T_H17 production) or forkhead box protein 3, which is essential for Treg cells.¹³ The development link between Treg and T_H17 cells might suggest that these T-cell subsets exist in equilibrium during inflammation and infection.

To summarize, Dectin-mediated fungal recognition preferentially triggers the differentiation of T_H17 cells, which produce IL-17A and IL-17F and also IL-22, all of which have a major role in immunity against *Candida* species (Fig 1).¹⁴ Although several knockout murine models indeed showed the role of these various components, this review will concentrate on human disorders in which defects in this pathway were found (Fig 1).

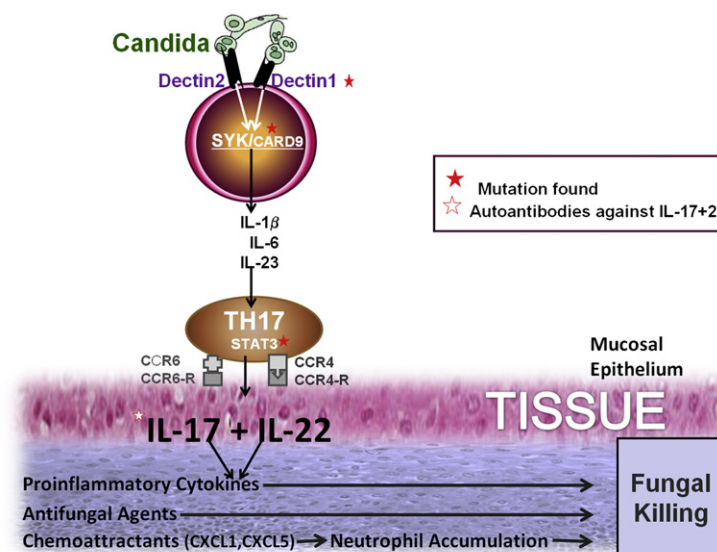


FIG 1. The immune response to *Candida* species infections. *Candida* species is recognized by several receptors, mainly Dectin-1 and Dectin-2, on the surfaces of macrophages. Binding of *Candida* species to its receptor will lead to intracellular signaling mediated by *CARD9*, which eventually will cause the production of IL-1 β , IL-6, and IL-23. These cytokines will interact with naive T_H cells and, through activation of STAT3, will differentiate to T_H17. T_H17 will produce IL-17A, IL-17F, and IL-22, which have various antifungal effects. Several mutations that have been described thus far are indicated in the figure.

TABLE I. Human disease associated with *Candida* species infection

Name	Frequency	Cause
Oral thrush in infancy	Very common	Normal immune response
Persistent oral thrush	Common	T-cell deficiency syndromes and HIV
Systemic candidiasis	Common	Immunocompromised patients and neutrophil dysfunction
HIES	Rare	<i>STAT3</i> mutation
APECED	Rare	Autoantibodies to IL-17A, IL-17F, and IL-22
Mendelian susceptibility to mycobacterial disease	Rare	Mutations in <i>IL12</i> and <i>IL12R</i>
Isolated mucocutaneous candidiasis, autosomal recessive and dominant forms	Rare	In rare cases there are mutations in <i>CARD9</i> , Dectin-1 (?), and <i>IL17RA</i> ; in most cases the cause is still unknown.

HUMAN CONDITIONS WITH SUSCEPTIBILITY TO MUCOCUTANEOUS CANDIDIASIS

For more information, see Table I. The most common *Candida* species infection in human subjects is the oral thrush, which essentially affects most infants around the age of 3 months. This is a self-limited benign condition and usually resolves after several days. Persistent or recurrent oral thrush should raise the possibility of a T-cell primary immunodeficiency, such as severe combined immunodeficiency or Di George syndrome. In adults persistent thrush is common in patients with HIV infection.

Autosomal dominant HIES

HIES is a rare multisystem disorder characterized by eczema, *Staphylococcus aureus*-induced skin abscesses, and pneumatocele formation affecting almost all patients. Recurrent mucocutaneous candidiasis is also a common clinical feature described in approximately 80% of these patients. Additional characteristic abnormalities recognized include multiple skeletal and connective tissue abnormalities, such as distinct facial features,

hyperextensible joints, pathological bone fractures, scoliosis, craniosynostosis, and retained primary teeth. Among the immunologic abnormalities are markedly increased IgE levels, which lead to the disorder named HIES. Heterozygous mutations of the gene encoding the transcription factor STAT3 have been identified as the cause of this syndrome.¹⁵ The mechanism by which mutations in *STAT3* cause this unique susceptibility to particular infections has recently begun to be defined. As previously described, *STAT3*-dependent signaling is crucial for the expression of ROR γ t, the transcription factor required for T_H17 cell line differentiation. Indeed, several studies documented an almost complete lack of circulating IL-17-producing T cells in patients with dominant negative *STAT3* mutations.¹⁶ Naïve T cells were unable to differentiate *in vitro* into memory CD4⁺/IL-17 T cells in response to various cytokines, and an impaired induction of *ROR* mRNA on stimulation was also observed. In patients with autosomal dominant HIES, the proportion of circulating CD4⁺/CCR6⁺ cells is low, which is consistent with CCR6 being a marker for IL-17-producing T cells. The levels of other cytokines (eg, IL-2 and IFN- γ) were not affected as much, suggesting T_H17-specific

differentiation impairment. Recently, it was found that T_H17 was also involved in the antifungal activity of saliva,¹⁷ which might lead to the commonly observed oral candidiasis seen in patients with HIES. Levels of several antifungal proteins, such as β -defensin 2 and histatins, were markedly decreased in the saliva of patients with HIES, and IL-17 significantly enhanced the expression of histatins.¹⁷

APECED syndrome

APECED syndrome is a rare, autosomal recessive, combined autoimmune and immunodeficiency syndrome arising from mutations in the autoimmune regulator gene (*AIRE*), leading to aberrant thymic self-tolerance mechanisms and the loss of thymic deletion of autoreactive T cells. It is characterized by multiorgan autoimmunity, mainly hypoparathyroidism and adrenal failure. Another major component of this syndrome is severe CMC, which remains localized to the mucosa and with no susceptibility to other overt infections.

Although the basis for the autoimmune disease tendency was clarified with the recognition of *AIRE* function, its relation to CMC has remained puzzling until the recently described neutralizing autoantibodies to T_H17 cytokines. Two articles published concomitantly in 2010 demonstrated high-titer neutralizing autoantibodies to the T-cell cytokines that regulate antifungal activity: IL-17 and IL-22. Puel et al¹⁸ and Kisard et al¹⁹ found high titers of autoantibodies against IL-17A, IL-17F, and/or IL-22 in the sera of almost all patients with APECED and CMC. The neutralizing function of the anti-IL-17A antibody was confirmed by inhibiting IL-6 production from IL-17-responsive fibroblasts. Thus anti-cytokine autoantibodies might be observed in patients with CMC associated with immune dysregulation entities and can inhibit the production of IL-6, IL-23, and TGF- β . A recent third study reported by Ng et al²⁰ assessing T_H17 responses on stimulation of PBMCs from patients with APECED with *Candida* species has demonstrated normal T_H17 cell proliferation and IL-17 production unless exposed to APECED plasma, which inhibited both functions in both the APECED and normal PBMCs. Characterizing anti-cytokine antibodies in patients with APECED might pave the way for new treatment modalities, such as the use of rituximab (anti-CD20).

IL-12p40 and IL-12 receptor β 1 deficiencies

Patients with IL-12p40 and IL-12 receptor β 1 deficiencies typically present with Mendelian susceptibility to mycobacterial disease clinically characterized by selective predisposition to mycobacterial and *Salmonella* species infections. However, around 25% of these patients also display a mild form of CMC. Interestingly, these patients have been shown to have a smaller proportion of circulating IL-17-producing T cells compared with healthy subjects, probably accounting for such susceptibility.²¹

Isolated CMC

Nonsyndromic CMC is characterized by an isolated susceptibility to candidiasis limited to the skin, nails, and mucous membranes, with no predisposition to invasive fungal disease or other pathogens and without autoimmune manifestations. Most cases are sporadic, but familial cases with autosomal dominant and recessive inheritance patterns have also been described.

Several hundred patients worldwide have been reported. Various defects in T-cell function were reported, but none could explain the unique susceptibility to *Candida* species infections in these patients.

Until recently, the genetic background to such cases has remained elusive. In 2009, the first autosomal recessive form of susceptibility to isolated CMC was reported.²² A homozygous point mutation in *CARD9* that results in a loss-of-function mutation caused by a premature termination codon (Q295X) was reported in a large, consanguineous, 5-generation Iranian family. Multiple members had recurrent peripheral fungal infections and all had a homozygous point mutation in *CARD9* and lacked wild-type expression of *CARD9* protein, whereas healthy family members had normal gene and protein expression. The *CARD9*-deficient patients also displayed a significantly smaller proportion of IL-17-expressing T cells and almost a complete defect in the generation of a T_H17 response. Experiments in the murine *CARD9*^{-/-} model showed that only wild-type *CARD9* and not the mutated human *CARD9* gene found, could restore cytokine production in response to the triggering of Dectin-1. In line with the critical role for Dectin/Syk/*CARD9*-signaling pathway in promoting proinflammatory cytokine production by dendritic cells, thereby inducing T_H17 cell line differentiation, these data again strengthen the evidence for a crucial role of T_H17 responses for host defense against mucosal *Candida* species infections.

As previously described, Dectin-1 plays a role in the immune response to *C. albicans*, and Dectin-1 knockout mice display a higher susceptibility to this fungus. An early stop codon polymorphism in Dectin-1 has been defined in a family with several members with mild CMC.²³ Macrophages of affected patients demonstrated a significantly lower fungal sensing capacity, but *in vitro* phagocytosis and intracellular killing were normal. Still, there is some doubt regarding Dectin-1 as a *bona fide* primary immunodeficiency: the family displayed a mild form of CMC, and Dectin-2 was found recently to be more important than Dectin-1.⁶ Furthermore, in the family described, both members with homozygous and heterozygous mutations had candidiasis, and finally, this polymorphism has been observed frequently in healthy donors from different ethnic populations, but the data regarding the prevalence of *Candida* species in these groups are not available. To summarize, the role of Dectin-1 deficiency in human subjects remains controversial. Most likely it constitutes a risk factor for mild forms of CMC.

Recently, Puel et al²⁴ described 2 families with primary CMC, one of which had a homozygous mutation in *IL17RA*, with the other having an autosomal dominant defect in *IL17F*. We have investigated another family with an autosomal dominant form of CMC who lacked IL-17 and T_H17 cells while the expression of *IL17* mRNA was completely normal (manuscript in preparation), pointing to a posttranscriptional defect. Still, it should be noted that these are rare cases of CMC in which the specific mutations were found, whereas in most cases, although an abnormal T_H17 production or function was observed,²⁵ the primary defect or defects leading to autosomal and recessive forms of isolated CMC are still unknown.

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