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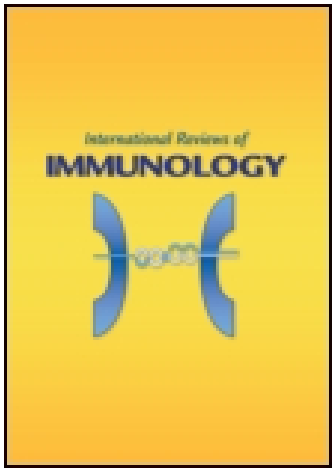

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The Evolving View of IL-17-Mediated Immunity in Defense Against Mucocutaneous Candidiasis in Humans

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REVIEW

The Evolving View of IL-17-Mediated Immunity in Defense Against Mucocutaneous Candidiasis in Humans

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The discovery of interleukin (IL)-17-mediated immunity has provided a robust framework upon which our current understanding of the mechanism involved in host defense against mucocutaneous candidiasis (CMC) has been built. Studies have shed light on how pattern recognition receptors expressed by innate immune cells recognize various components of *Candida* cell wall. Inborn errors of immunity affecting IL-17+ T cell differentiation have recently been defined, such as deficiencies of signal transducer and activator of transcription (STAT)3, STAT1, IL-12Rβ1 and IL-12p40, and caspase recruitment domain 9. Impaired receptor-ligand coupling was identified in patients with IL-17F and IL-17 receptor A (IL17RA) deficiency and autoimmune polyendocrine syndrome (APS) type 1. Mutation in the nuclear factor kappa B activator (ACT) 1 was described as a cause of impaired IL-17R-mediated signaling. CMC may be part of a complex clinical phenotype like in patients with deficiencies of STAT3, IL-12Rβ1/IL-12p40 and APS-1 or may be the only or dominant phenotypic manifestation of disease which is referred to as CMC disease. CMCD may result from deficiencies of STAT1, IL-17F, IL-17RA and ACT1. In this review we discuss how recent research on IL-17-mediated immunity shed light on host defense against mucocutaneous infection by *Candida* and how the discovery of various germ-line mutations and the characterization of associated clinical phenotypes have provided insights into the role of CD4+IL-17+ lymphocytes in the regulation of anticandidal defense of body surfaces.

Keywords: *Candida*, interleukin-17, interleukin-17 receptor-mediated signaling, mucocutaneous candidiasis disease, pattern-recognition receptors, signal transducer and activator of transcription

INTRODUCTION

Colonizing *Candida* may gain access to the circulation and cause invasive bloodstream infection or organ diseases, including hepato-splenic candidiasis and candida nephritis [1]. Invasive candidiasis typically occur in hemato-oncology patients and in those with long-term therapy at intensive care unit [2, 3]. In addition, patients with chronic granulomatous disease or other primary defects of phagocytic cell function, as well as those with quantitative deficiency of the phagocytic cell pool also predispose to invasive candidiasis [4, 5]. In contrast, superficial or chronic mucocutaneous

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candidiasis (CMC) occurs at body surfaces as vulvovaginal, oropharyngeal or esophageal candidiasis [6–8]. Several primary immunodeficiency disorders (PIDs) typically characterized by CMC and impaired IL-17-mediated immunity have been identified recently [9]. CMC in such patients may be part of a complex clinical phenotype exemplified by dominant negative signal transducer and activator of transcription (STAT)3 deficiency, interleukin (IL)-12Rβ1 and IL-12p40 deficiencies, and autoimmune polyendocrine syndrome (APS) type 1 [10–13]. In a subgroup of PIDs, predisposition to superficial candidiasis may be the only or the dominant characteristic of the underlying genetic disorder (CMC disease, CMCD) [9]. The first CMCD was described in 2011 by two groups reporting on 21 unrelated families and 61 patients carrying germline missense mutation in the coiled-coil domain (CCD) of *STAT1* [14, 15]. One of these groups also reported on impaired differentiation of naïve CD4+ T cells into IL-17+ lymphocytes due to gain of function (GOF) and gain of phosphorylation of *STAT1* in a large number of patients with CMCD [14]. Subsequently, *STAT1* GOF mutation associated with CMC was found by several groups [16–21]. Primary genetic defects of the IL-17 cytokine-IL-17R coupling and IL-17R signaling were also reported as causes of CMCD [22, 23]. In particular, autosomal dominant IL-17F deficiency, autosomal recessive IL-17RA deficiency, and signaling defect due to mutation in the gene of nuclear factor kappa B (NF-κB) activator (ACT1) were described. In this review, we discuss recent developments that have increased our understanding of the immunological and genetic basis of CMC. Molecular mechanisms that may be involved in the unique and exceptional tropism of *Candida*, especially *Candida albicans,* at the mucosal epithelium will be discussed. Effector functions of CD4+IL17+ T cells will be reviewed in the context of host defense against infection by *Candida* at mucosal surfaces. Finally, we will discuss inborn errors of IL-17-mediated immunity that may lead to CMC in humans.

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Candida as a Unique Fungal Commensal in Humans

Candida, Aspergillus and Cryptococcus are the three major opportunistic fungal species. *Candida,* especially *C. albicans* stands out as the most common fungal pathogen in humans. In healthy individuals, *C. albicans* adheres to the mucosal epithelium and skin which is usually symptomless as an established commensalism [24, 25]. In patients with impaired anticandidal host defense, however, these fungi may cause persistent and recurrent superficial infection and epithelial cell damage which may be recalcitrant to therapy.

The precise mechanism of commensalism by *C. albicans* is not completely understood [25, 26]. To establish colonization *Candida* must have developed the unique ability to adhere to epithelial cells so that to avoid being washed away by food and mucosal secretion. *Candida* should also be able to compete with other colonizing agents like bacteria in the gastrointestinal tract. Furthermore, *Candida* should be able to survive a large array of host immune and non-immune defenses at mucosal surfaces. Although the commensal phase itself is generally considered harmless, it may develop into CMC and invasive candidiasis, which is referred to as the pathogenic phase of *C. albicans*. Symptomatic damage of the mucosal epithelium is characteristic for the pathogenic phase, but asymptomatic damage may also occur during the commensal phase [26, 27].

Candida species "appear to know something" that remains to be elucidated by scientists searching for a better understanding of host defense against these fungi. It is intriguing that among the *Candida* species only a few colonize the mucocutaneous surfaces and associate with human disease [27, 28]. *C. albicans* may especially closely associate to humans in contrast to other fungi. Commensal colonization of *Candida* is a remarkable condition because the vast majority of both CMC and invasive

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candidiasis are of endogenous origin [28]. Invasive candidal disease may be caused by various non-albicans *Candida* like *C. glabrata*, *C. tropicalis* and *C. parapsilosis*. However, *C. albicans* is the most common species isolated from patients with CMC. One possible explanation may be that *C. albicans,* in contrast to non-albicans species, grow hyphae that invade and penetrate epithelial cells more aggressively than yeasts. Experimental data suggest that formation of hyphae may be related to virulence of *C. albicans* and possibly *C. dubliniensis* which is also known to form hyphae [29]. Major *Candida* adhesins including hyphal wall protein (Hwp) 1 that binds trans-glutaminase, and the agglutinin-like sequence (Als) 3 that binds host cell cadherin may play a role for epithelial binding [30, 31]. That, *Candida* adhesins may be important to establish epithelial damage is supported by the observation that deletion of genes encoding for *Hwp1* or *Als3* result in remarkable decrease of adhesion to epithelial cells. Other adhesins on hyphae may recognize arginine-glycine-aspartic acid (RGD) sequences on epithelial cells and several extracellular matrix proteins [32]. Integrin-like protein (INT) 1 may recognize RGD-containing proteins. This candidal adhesin is homologous to mammalian integrins and itself contains an RGD site that may be recognized by integrins on human cells, facilitating further the adhesion of *Candida* to the cell surface [32]. These findings provide further explanation for the unique symbiosis of *Candida* with humans and the tropism of these fungi to mucosal epithelium. Whether *Candida* remains a silent and innocent colonizer or becomes an aggressive mucosal or invasive pathogen depends largely on the ability of the host to mount an efficient IL-17-mediated effector immunity.

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Th17 Cells as Major Players of Host Defense against *Candida* at Mucosal Surfaces

A subset of CD4+ helper T cells typically produce IL-17A-type cytokines including IL-17A-E and IL-22 and are referred to as Th17 cells or CD4+IL-17+ T cells [33]. Th17 cytokines are important for the prevention of infection with *Candida* colonizing the mucocutaneous surfaces [9] (Fig. 1). The differentiation, expansion and maintenance of human IL-17-producing T cells are induced by a set of cytokines, including IL-1β, IL-6, IL-21, IL-23 and probably TGF-β, and transcription factors such as STAT3, retinoic acid-related orphan receptor (ROR)-γt and interferon regulatory factor 4 [33–37] (Fig. 1). IL-17A is produced not only by conventional CD4+IL-17+ T helper cells, but also by $\gamma\delta$ T cells and innate lymphoid cells [38, 39].

Over the past decade our understanding of IL-17+ T lymphocyte-mediated immunity has paralleled with a better understanding of host defense against *Candida* of body surfaces. The discovery that CD4+ T cell may be induced by IL-1β and IL-6 toward a CD4+ T cell subset producing IL-17 (CD4+IL17+ cells) opened a new avenue of intensive research into the pathology of various inflammatory conditions and host defense mechanisms against *Candida* [40].

Induction of Th17 Differentiation by Pattern Recognition Receptors

The differentiation of naïve CD4+ T-helper cells into IL-17-producing T cells and the development of effective mucosal immunity against fungi may be initiated by binding of *Candida* to innate immune cells via pattern recognition receptors (PRRs). These receptors including toll-like receptor (TLR) 2, TLR4, the macrophage mannose receptor (MR), dectin-1, dectin-2 and the macrophage-inducible C-type lectin (MINCLE) may bind pathogen-associated molecular patterns such as fungal mannoproteins and β-glucans [41–45].

Recognition of mannoproteins and glycans by PRRs have been implicated to play a role in host defense against *Candida* and innate defense mechanisms were proposed to shape the adaptive responses by promotion of skewing CD4+ T cells into Th17 lineage [42, 45, 46]. TLR2 and TLR4 may bind *Candida* but it was poorly defined how

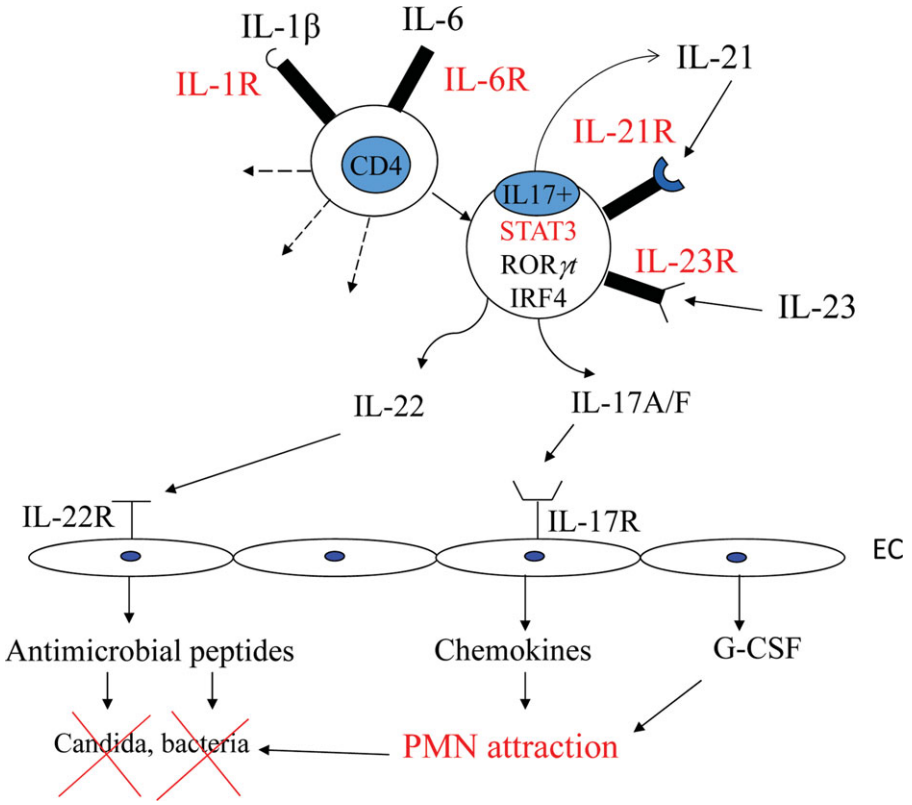

FIGURE 1. Schematic representation of IL-17+ T cell differentiation and function. The differentiation of naïve $CD4^+$ T cells into CD4+IL-17+ cells is driven by the combined action of cytokines such as IL-1β, IL-6, IL-21 and IL-23. Transcription factors, including signal transducer and activator of transcription (STAT) 3, retinoic acid-related orphan receptor (ROR) γt and interferon regulatory factor (IRF) 4 are also involved in inducing IL-17+ T cell differentiation. The release of IL-17-family cytokines such as IL-17A/F and IL-22 is a key element of host defense against fungi and bacteria, because these cytokines induce the secretion of various growth factors, chemokines and antimicrobial peptides by epithelial cells. The accumulation of professional phagocytes and antimicrobial peptides at the site of invasion results in the elimination of fungal and bacterial pathogens. EC, epithelial cells; G-CSF, granulocyte colony-stimulating factor; PMN, polymorphonuclear neutrophil. Adapted from [9, 37].

these interactions alter host defense mechanisms [41]. Contradicting data were reported in mice and humans regarding the role of TLR-mediated immunity to *Candida* and it appears that myeloid differentiation factor (MyD) 88 deficiency do not predispose humans, in contrast to mice to infections by this fungal pathogen [47, 48]. For example, $TLR4^{-/-}$ mice exhibited increased susceptibility to invasive candidiasis, whereas $TLR2^{-/-}$ mice were more resistant to *Candida* [49, 50].

The macrophage MR, one of the best characterized C-type lectin receptor (CLR) was the first membrane receptor implicated in the recognition of *Candida* yeasts by human macrophages [43, 44, 51–53]. Monocyte-derived human macrophages (MDM) ingested and killed unopsonized *Candida* blastoconidia but both phagocytosis and killing of unopsonized yeasts were slower than those of serum-opsonized *Candida* [42]. Furthermore, unopsonized *Candida* evoked negligible release of toxic oxygen radicals compared to the robust generation of these agents by serum-opsonized yeasts [42]. These data suggested that the macrophage MR-mediated uptake of *Candida* yeast could play a role in elimination of these fungi in tissue environments which are poor

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in opsonising serum such as the subepithelial compartment and body surfaces. Human blood mononuclear cells could be induced to differentiate into IL-17+ cells by mannan but not by β-glucan or chitin indicating a role for the MR in shaping IL-17-mediated immunity [46]. In addition, MR-dependent production of IL-17 by cells from dectin-1 deficient patients was reported suggesting the role of the MR but not of dectin-1 in the generation of IL-17 cellular responses [46]. Thus, the role that dectin-1 may play in defense against *Candida* in mice remains to be further defined in humans.

Dectin-2 receptors primarily recognise *N*-linked mannan exposed on the surface of *Candida* and in particular, recognise hyphae rather than yeasts and may be more relevant innate immune sensors in recognition of *Candida* than dectin-1 [54]. We believe that multiple cell-fungal interactions may be required to initiate and mount predominantly Th17 differentiation and the relative role of various PRRs in this complex immunopathological process should be the focus of further research. For example, primary deficiency of caspase recruitment domain (CARD) 9 involved in signaling by different lectin receptors was described in a large Iranian family and was proposed to predispose patients to CMC [55]. However, two of the eight patients reported in this family also had invasive candidiasis and two of the patients had no proven candidal disease. More intriguingly, several patients with invasive infections caused by dermatophytes but not *Candida* have been reported recently [56–58]. Thus, the expanding spectrum of clinical phenotype in patients with CARD9 deficiency makes a direct relationship between CMC and this PID to be further elucidated.

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Inborn Errors of Th17-mediated Immunity in Humans

Experiments in nature suggest that patients with germ line mutations in *STAT3* resulting in the complex clinical phenotype of hyper-IgE syndrome (HIES), *AIRE* mutation causing APS-1 and IL12Rβ1 deficiency causing increased susceptibility to atypical *Mycobacteria* and *Salmonella* are also susceptible to CMC [9–13]. Patients with these PIDs present with an impaired differentiation of IL17+CD4+ T cells (HIES and IL12Rβ1 deficiency) or increased production of anti-IL-17 antibodies (APS-1). *STAT1* GOF mutation was also reported to interfere with Th17 differentiation and turned out to be the most common cause of isolated CMC (CMC disease, CMCD) [14–21]. Sporadic cases of CMCD caused by germ line mutations of *IL17F*, *IL17RA* and *ACT1* and characterized by impaired stimulus-response coupling and signaling via the IL17R were also reported [22, 23].

The milestone discovery of the genetic cause of autosomal dominant HIES

HIES (Job's syndrome) is a complex PID characterized by skin and lung infections caused predominantly by *Staphylococcus aureus* and *C. albicans*, pneumatocele formation, severe eczema and extreme elevation of serum IgE [10, 59–61]. Distinctive facial features, hyperextensibility of the joints, cranial synostosis, scoliosis, abnormal dentition and predisposition to pathological fractures add to the multisystem phenotype of HIES. Staphylococcal skin abscesses typically fail to demonstrate erythema and warmth, and hence are called "cold abscesses" [59].

The first breakthrough in our understanding of the role of IL-17-mediated immunity in host defense against *Candida* of mucocutaneous surfaces was achieved by the discovery of the genetic basis of HIES. In 2007, two independent groups reported mutation in *STAT3* as a major cause of autosomal dominant (AD) and sporadic HIES [62, 63]. Mutations were localized in either the DNA-binding domain (DBD) or the SH2 domain of STAT3 but later were described throughout the gene and in different ethnic groups [64, 65]. Severe Th17 cell depletion was also reported in AD and sporadic HIES patients with STAT3 dominant negative mutation [66–68]. This observation was in con-

cert with the recognition of STAT3 as a transcription factor involved in differentiation of CD4+ cells into a CD4+IL-17+ lineage (Fig. 1).

STAT3 is a transcription factor involved in signaling for a variety of cytokines, hormones and growth factors which may explain the complex clinical phenotype and multiple organ involvement in HIES patients [69, 70]. STAT3 plays important roles in maturation, differentiation and function of T and B cells [71, 72]. In addition to its involvement in Th17 cell differentiation, induction of CD4+ T cells toward the follicular helper T cell lineage may also depend on STAT3 [73]. Patients with dominant negative STAT3 mutation present with a decreased number of central memory CD4+ and CD8+ lymphocytes and an increased number of naïve T cells [74]. Due to this memory, T cell defect patients with HIES are predisposed to develop varicella zoster virus reactivation and prolonged Epstein-Barr virus viremia.

The impaired IL-17+ T cell differentiation and function may be a plausible explanation for the susceptibility of HIES patients to CMC [9]. However, such patients are also susceptible to infections by pyogenic bacteria, especially *S. aureus* causing recurrent skin and lung infections [37, 60, 61]. Alternative mechanisms responsible for the unique vulnerability to infection of the skin, mucous membranes and the lung in HIES patients may exist. In patients with oropharyngeal thrush a significant impairement in salivary antimicrobial proteins such as β-defensin 2 was found [75, 76]. The defective salivary gland activity may be related to the reduced candidacidal activity of saliva and *Candida* colonization of the mucosa at least in the oropharynx. In addition, defective responses of keratinocytes and bronchial epithelial cells to IL-17 was reported as a possible additional mechanism responsible for the impaired host defense to Candida by HIES patients [68]. Cells from HIES patients were more dependent than from healthy controls on the synergistic effect of Th17-derived cytokines and classical proinflammatory cytokines such as IL-1β in their production of chemokines and antimicrobial peptides.

Discovery of STAT1 GOF mutation as the most common cause of CMC

The signaling pathway triggered by the engagement of interferons (IFN-γ, IFN-α/β) and IL-27 with their specific cell surface receptors have been extensively studied and provided knowledge of the intracellular machinery that include a predominant activation of *STAT1*. Loss of function (LOF) mutations in *STAT1* were reported to associate with various infections through mechanisms involving impaired IFN-γ and IFN-α/β immunity [71, 77]. Complete and partial recessive mutations in *STAT1* were described to result in an increased susceptibility to mycobacterial and viral diseases because of impaired responses to both IFN-γ and IFN-α/β [77]. In contrast, heterozygous dominant negative mutation in *STAT1* cause susceptibility to mild mycobacterial infection because of impaired response to IFN-γ but not to IFN-α/β. Recently heterozygous GOF mutation causing impaired development of IL-17+ T cells from CD4+ T cells were described in patients with CMC [14, 15]. These GOF mutations resulted in increased phosphorylation, DNA binding, transactivation, and interaction with protein inhibitor of activated STAT (PIAS), and decreased dephosphorylation of *STAT1* [14, 78]. Thus, the poor development of IL-17+ T cells, and as a consequence CMC may involve increased responses to IFN-γ, IFN-α/β and IL-27, which are STAT1-dependent repressors of IL-17-producing cells. *STAT1* GOF mutation was first discovered by whole-exome sequencing in a Ukrainian patient with CMCD [14, 35]. CCD and DBD mutations were subsequently found in a large number of patients in other kindreds [14–21]. Over the past few years, GOF mutations of *STAT1* have been proved to be the most common etiology of CMC. Heterozygous dominant *STAT1* GOF mutation may lead to stronger cellular responses to STAT1-dependent IL-17 inhibitors

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(IFN-α/β, IFN-γ and IL-27) [14]. This would account for the impaired IL-17+ T-cell development with an impact on IL-17+ T cell-mediated antifungal responses.

Infectious etiologies which were also described in association with *STAT1* GOF mutation include *Histoplasma capsulatum*, *Coccidioides immitis*, *Apophysomyces trapeziformis*, orf virus, *Penicillium marneffei* and *Fusarium solani* [17, 78–82]. Patients with *STAT1* GOF mutations may display herpes reactivation diseases in addition to CMCD [17]. The recurrent herpes virus disease observed in some patients with such mutations may be due to the impaired development and maintenance of central memory T cells, as in patients with heterozygous *STAT3* mutations and AD HIES [83].

Deficient functioning of the IFN-γ/IL-12 pathway was found to associate with invasive infection by dimorph endemic fungi like *Histoplasma capsulatum* and *Coccidioides immitis* [84, 85]. Five patients with *STAT1* GOF mutation were also identified with invasive histoplasmosis and CMC (3 patients) and coccidioidomycosis without CMC (2 patients) [78]. The heterozygous missense mutations affecting the CCD or DBD of *STAT1* resulted in lower *STAT1* methylation, enhanced *STAT1*/protein inhibitor of activated *STAT1* (PIAS) association, increased IFN-γ-induced gene expression, and impaired responses to IFN-γ restimulation. This report and other studies suggested the intriguing possibility of functional overlap of GOF and LOF mutations of *STAT1*.

STAT1 GOF mutation has been identified in a 24-year-old male patient with disseminated mucormycosis caused by *Apophysomyces trapesiformis* [79]. This patient never had CMC or autoimmunity and he had no predisposing condition to mucormycosis, such as penetrating trauma, diabetes mellitus or hemochromatosis. Thus, *A. trapesiformis* and other members of the *Mucorales* species may cause infections in patients with *STAT1* GOF mutation. Mucormycosis may be a heralding infectious manifestation of this genetic disorder before the occurrence of CMC.

A 34-year-old male patient with a previous history of recurrent and persistent candidiasis of the skin, nails, and mucosal surfaces starting at 2 years of age developed orf, a viral zoonotic disease, caused by *Parapoxvirus* [80]. Genetic analysis of this patient and his 6-year-old son who had been also suffering from CMC since birth, revealed heterozygous c.820G>A *STAT1* mutation (R274W). This mutation was previously found to result in *STAT1* GOF including enhanced phosphorylation and DNA-binding, and impaired differentiation of CD4+ T cells into IL-17+ cells [14, 17]. In contrast to other patients carrying the R274W mutation the index patient (but not his son) also had severe CD4 lymphopenia, low levels of IgG2 and IgG4 subclasses and recurrent bacterial pneumonias since 15 years of age. He was treated with regular IVIG infusions. The giant orf lesion on his hand was successfully cured with cidofovir. His disease course was complicated with Coombs positive hemolytic anemia, autoimmune hepatitis, hypothyroidism and pulmonary embolia. Despite successful hematopoietic stem cell transplantation performed at age 35 he died because of bleeding from an intracranial mycotic aneurism, a well-defined complication in patients with CMC [14, 21]. It remains unclear whether impaired Th17 immunity played any role in the development of orf in this patient. This report nevertheless raises the possibility that *STAT1* GOF mutation may predispose to DNA viral disease other than recurrent varicella and HSV, described before in two patients also carrying the R274W mutation [17].

STAT1 GOF mutation associated with CMC and invasive infection by *Penicillium marneffey* was reported in three Chinese patients [81]. Lymphocytes from two of these patients exhibited defective IFN-γ production upon stimulation with *P. marneffey* in vitro. The authors suggested that the combined primary defect in IFN-γ an IL-17 immune responses may be responsible for infection by this filamentous mold. This report further extends the spectrum of infections occurring in patients in *STAT1* GOF

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mutation. It also suggests that the phenotypic expression of *STAT1* GOF mutation may be wider than it was previously thought.

Another chronic fungal infections associated with a previously described *STAT1* GOF mutation was found in a Chinese patients with infection by *Fusarium solani* [82]. This patient was free of CMC or invasive candidal disease. This report further confirms the possibility that *STAT1* GOF mutation may predispose patients to a wide range of infections including various fungal disease.

Predisposition to CMC in patients with IL12Rβ1 and IL-12p40 deficiency

IL-12 and IL-23 are heterodimeric cytokines compose of p35 and p19 subunits, respectively, and share a p40 subunit [86, 87]. The disulphide-bond 35 kD and 40 kD subunits of IL-12 produced primarily by professional antigen presenting cells bind to the IL-12 Rβ1/IL-12Rβ2 receptor complex [88]. IL-12 induces the production of IFN-γ by NK cells and T cells (Fig. 2) and drive CD4+ T cells to differentiate into Th1 phenotype [88, 89]. High-affinity binding of IL-12 to its receptor requires both IL-12Rβ1 and IL-12Rβ2 chains but gene expression studies suggested that the IL-12Rβ1 is primarily responsible for IL-12 binding whereas IL-12Rβ2 is mediating signaling [88]. On the other hand, the p19–p40 heterodimer of IL-23 also binds to IL-12Rβ1 but not to the β2 chain and uses its own receptor complex composed of IL-12Rβ1 and IL-23R on T cells and NK cells [90, 91]. IL-23 is a key cytokine to maintain expansion of CD4+IL17+ T cells that differentiate from naïve CD4+ cells upon exposure to IL-1β, IL-6 and IL-21 [33, 92]. Unsurprisingly, the functional impairment of IL-12Rβ1 was found to result in a wide range of infections caused predominantly by intracellular pathogens [93–98]. T cells and NK cells from patients with IL-12Rβ1 mutation cannot respond to IL-12 or IL-23 because these cytokines bind to IL-12Rβ1 and these patients frequently develop CMC [11]. T cells and NK cells from patients with deficiency of the IL-12p40 subunit shared by IL-12 and IL-23 may also be susceptible to CMC because of the impaired maintenance of IL17+ T cells at mucosal surfaces. In contrast, patients with various genetic forms IFN-γR deficiency do not display CMC [93]. Instead, they present with Mendelian susceptibility to mycobacterial disease.

Analyses of 156 patients with IL-12Rβ1 deficiency showed that 35 (23%) of such patients presented with clinical features of candidiasis [11]. Most patients were identified with recurrent and persistent CMC and candidiasis was the first documented clinical manifestation in 19 of 35 patients despite vaccination of 10 of these 19 patients with live bacille Calmette-Guérin vaccine. Most candidiasis episodes were mucocutaneous, oropharyngeal candidiasis being the most common, with esophageal, cutaneous and genital candidiasis also being recorded. In addition to mucosal or cutaneous fungal diseases, five episodes of invasive candidiasis affecting four patients were found. Intriguingly, in some patients the first episodes of candidiasis occurred before mycobacterial disease or salmonellosis were documented.

CMC was also observed in 3 (6.7%) of 49 patients with autosomal recessive IL-12p40 deficiency [12]. One patient had invasive candidiasis and two presented with oral thrush. The immunological basis of the remarkably lower incidence of CMC in patients with IL-12p40 deficiency compared to that found in patients with IL-12Rβ1 deficiency is not completely understood.

Revealing germ-line IL17F, IL17RA and ACT1 mutations in patients with CMCD

The binding of IL-17A and IL-17F to their receptors induces diverse signaling pathways and results in the secretion of antimicrobial peptides, tumor necrosis factor (TNF)-α, IL-6, IL-8, CXCL-1, CCL20, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [99–102]. These cytokines and chemokines recruit and activate polymorphonuclear neutrophil

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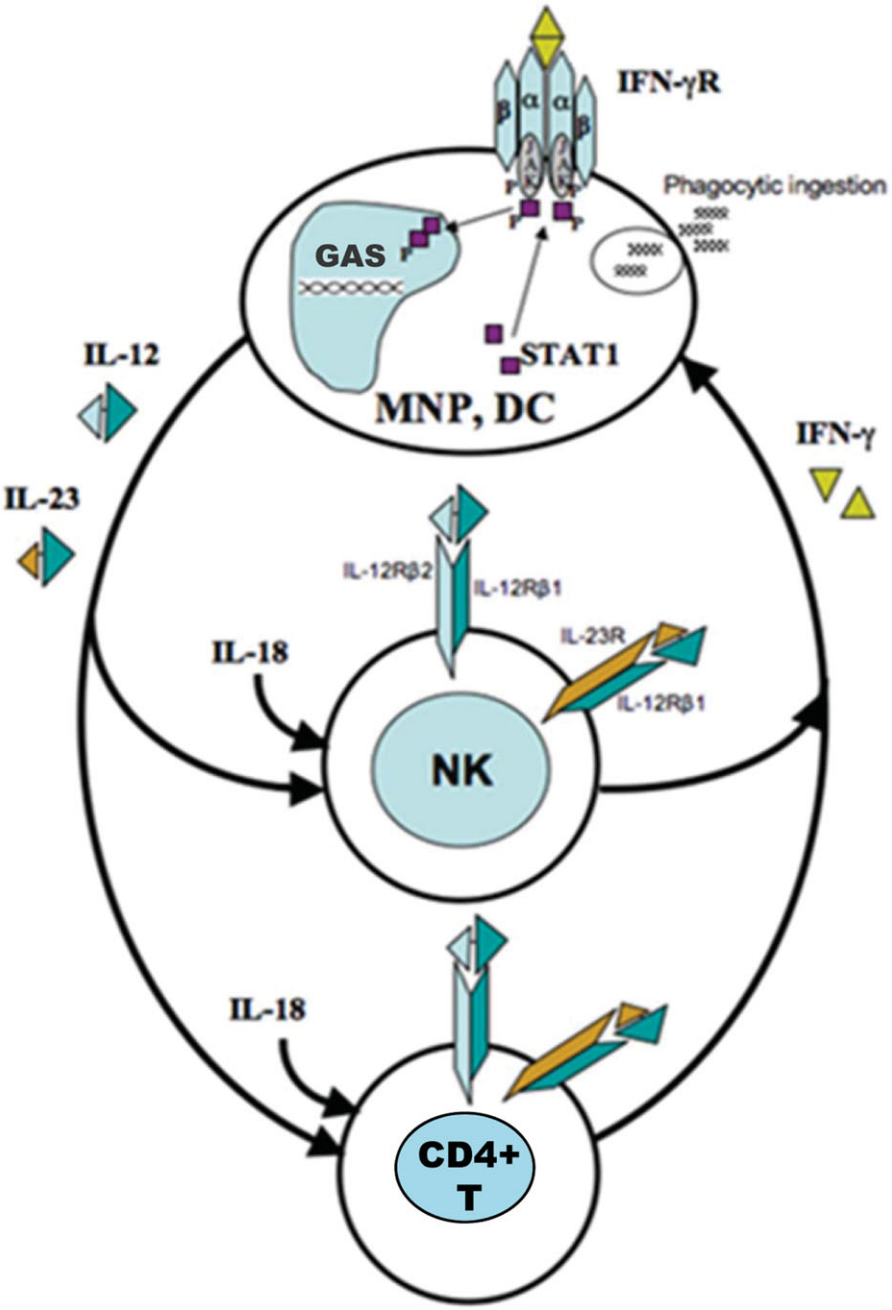

FIGURE 2. Schematic representation of the interleukin (IL)-12/interferon (IFN) γ circuit. Upon ingestion of pathogens by mononuclear phagocytes (MNP), dentritic cells (DCs) IL-12 and IL-23 are produced, which in turn will induce the production of IFN-γ by natural killer (NK) cells and CD4+ T cells. IL-18 also induces the release of IFN-γ by NK cells and T cells. IFN-γ binds to its cell-surface receptor that consists of two heterodimeric subunits IFNγRα (or IFNGR1) and IFNγRβ (or IFNGR2) chains, which are coupled with Janus-associated kinase (JAK) 1 and JAK2. IFN-γ binding results in dimerization of the two receptor subunits and phosphorylation of JAK1 and JAK2. Activated JAKs phosphorylate IFNGR1 leading to recruitment and activation of signal transducer and activator of transcription (STAT) 1 proteins that translocate to the nucleus and binds to interferon-gamma-activated sequences (GAS) of IFN-γ-inducible genes which are then transcribed. Adapted from [9].

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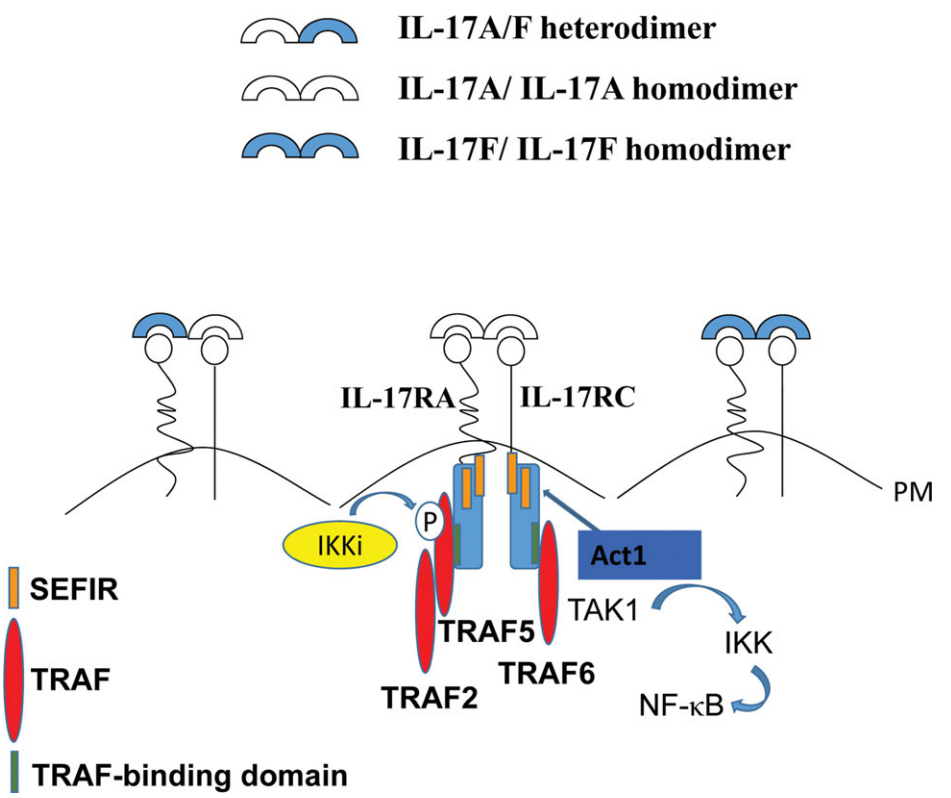

FIGURE 3. Schematic representation of the IL-17/ IL-17R coupling and IL17R-mediated signaling. IL-17A and IL-17F heterodimers or homodimers are recognized by the plasma membrane (PM)-localized IL-17RA/IL-17RC heteromeric receptor complex. Upon ligand binding, IL-17R will recruit the adaptor molecule NF-κB activator (ACT) 1 by homotypical interactions between their respective SEFIR domains. TRAF6 and TAK1 binding in turn will activate the IKK complex and induce NF-κB activation. ACT1 may also associate with IKKi and subsequently activate TRAF2 and TRAF5. SEFIR, similar expression to fibroblast growth factor (SER)/IL-17R domain; TRAF, tumor necrosis factor receptor-associated factor; IKK, inhibitor of NF-κB kinase; IKKi, inducible IKK; TAK, transforming growth factor beta-activated kinase. Adapted from [9].

granulocytes, providing protection against diverse infectious agents in the environment (Fig. 1). Downstream signaling activated by IL-17R binding to its ligands include the adaptor protein ACT1 [100–103]. IL-17A and IL-17F form heterodimers and homodimers and signal through a heteromeric receptor complex of two IL-17R chains: IL-17RA and IL-17RC (Fig. 3) [101, 103]. Receptor ligand coupling will subsequently result in recruitment of ACT1 [104]. Both IL-17R chains and ACT1 contain a conserved SEFIR domain and binding of these proteins occurs via homotypical interactions between their respective SEFIR domains (Fig. 3). The E3 ubiquitine ligase TRAF6 binds then to ACT1 and mediates downstream signaling [103–105]. Ubiquitination of TRAF6 by ACT1 will trigger recruitment of TAK1 and the TAK1 binding partner molecules and induce NF-κB activation (Fig. 3). ACT1 may also form a complex with the inducible kinase IKKi which will phosphorylate ACT1 and generate docking sites for the adaptors TRAF2 and TRAF5 [100, 102].

The most compelling evidence that isolated CMC is truly a PID was provided by analyses of patients with recurrent or persistent *Candida* infections and AD IL-17F deficiency or autosomal recessive IL-17RA deficiency [22]. One of the published cases, a

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Moroccan boy, was born to consanguineous parents and was found to carry a homozygous c.850C > T mutation in the *IL17RA* gene, resulting in the creation of a premature stop codon (Q284X) in the part of the gene corresponding to the extracellular domain of the receptor. This mutation abolished responses to IL-17A and IL-17F, due to a complete loss of IL-17RA protein expression on the patient's cells. The parents and siblings of this patient were all healthy and heterozygous for this mutation [22].

The other patients, from a multiplex Argentinean family, had a c.284C>T heterozygous mutation in the *IL17F* gene, predicting the replacement of serine residue with a leucine residue in position 65. This mutation was shown to be severely hypomorphic and dominant, as it affected the function of both homo- and heterodimers containing the mutant isoform, by impairing their binding to the receptor [22]. These observations clearly support the concept that CMC disease may occur as a result of inborn errors of IL-17-mediated immunity.

Biallelic missense mutation in the adaptor protein ACT1 and CMC in two siblings was reported [106]. The T536I mutation affected the SEFIR domain and abolished homotypic interaction between ACT1 and the IL-17R chains. This mutation also abolished responses of patients' fibroblasts to IL-17A and IL-17F and of T cells to IL-17E. In contrast to SEFIR-dependent interactions, binding of ACT1 to other proteins like CD40, heat shock protein (HSP) 70 and HSP90 remained intact.

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CONCLUSION

C. albicans is a unique commensal at mucosal surfaces in humans and several PRRs of innate immune cells were implicated in binding *Candida* yeasts and hyphae. In particular, the role of PRRs in inducing Th17 cell differentiation from naïve CD4+ cells has been proposed but the precise mechanism of IL-17 induction has only been vaguely defined. Until the discovery of *STAT3* dominant negative mutation causing severe defect of Th17 cell differentiation, our understanding of the mechanisms involved in host mucosal responses in humans to *Candida* was poor. Recent advances in our understanding of genetic etiologies of several PIDs such as *STAT3* mutation in patients with AD and sporadic HIES, and *STAT1* GOF mutation causing CMCD elucidated significantly our knowledge of anticandidal immunity of mucosal surfaces. Discoveries of *IL17F*, *IL17RA* and *ACT1* mutations in association with CMCD enlightened further the mechanisms underlying CMC in patients with PIDs and have revealed that human IL-17+ T-cell immunity is critical for mucocutaneous host defense against *Candida* in natural conditions. More research is required to define precisely the mechanisms by which IL-17+ T cells contribute to the elimination of candidal and bacterial infections at body surfaces. Such studies should take into account the disease-modifying factors responsible for the severity and variability of the phenotypes of PIDs associated with IL-17+ T cell-mediated immune defects.

ABBREVIATIONS

ACT	NF-κB activator
AD	autosomal dominant
Als	agglutinin-like sequence
APS	autoimmune polyendocrine syndrome
AR	autosomal recessive
CARD	caspase recruitment domain
CCD	coiled-coil domain
CLR	C-type lectin receptor
CMC	mucocutaneous candidiasis

CMCD	CMC disease
DC	dentritic cell
DBD	DNA-binding domain
EC	epithelial cell
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GOF	gain of function
HIES	hyper-IgE syndrome
Hwp	hyphal wall protein
HSP	heat-shock protein
IFN	interferon
IKK	inhibitor of NF-κB
IKKi	inducible IKK
IL	interleukin
INT	integrin-like protein
IRF	interferon regulatory factors
ISRE	interferon-stimulated response element
JAK	Janus-associated kinase
LOF	loss-of-function
MDM	monocyte-derived macrophage
MINCLE	macrophage-inducible C-type lectin
MR	mannose receptor
NF-κB	nuclear factor kappa B
NK	natural killer
MyD	myeloid differentiation factor
PAMP	pathogen-associated molecular pattern
PIAS	protein inhibiting activated STAT1
PID	primary immunodeficiency disorder
PMN	polymorphonuclear neutrophil
PRR	pattern recognition receptor
RGD	arginine-glycine-aspartic acid
ROR	retinoic acid-related orphan receptor
SEFIR	similar expression to fibroblast growth factor (SER)/IL-17R domain
STAT	signal transducer and activator of transcription
TAK	transforming growth factor beta-activated kinase
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRAF	TNF receptor associated factor

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Declaration of Interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

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REFERENCES

[1] Maródi L. Local and systemic host defense mechanisms against Candida: immunopathology of candidal infections. Pediatr Infect Dis J 1997;16:795–801.

[2] Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. Crit Rev Microbiol 2010;36:1–53.

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[3] Maródi L, Johnston RB Jr. Invasive Candida species disease in infants and children: occurrence, risk factors, management, and innate host defense mechanisms. Curr Opin Pediatr 2007;19:693–697.
[4] Fleischmann J, Church JA, Lehrer RI. Primary Candida meningitis and chronic granulomatous disease. Am J Med Sci 1986;291:334–341.
[5] Donini M, Fontana S, Savoldi G, et al. G-CSF treatment of severe congenital neutropenia reverses neutropenia but does not correct the underlying functional deficiency of the neutrophil in defending against microorganisms. Blood 2007;109:4716–4723.
[6] Cassone A. Vulvovaginal Candida albicans infections: pathogenesis, immunity and vaccine prospects. BJOG-Int J Obstet GY 2014. doi:10.1111/1471-0528.12994.
[7] Conti HR, Peterson AC, Brane L, et al. Oral-resident natural Th17 cells and $\gamma\delta$ T cells control opportunistic Candida albicans infections. J Exp Med 2014;211:2075–2084.
[8] de Repentigny L, Lewandowski D, Jolicoeur P. Immunopathogenesis of oropharyngeal candidiasis in human immunodeficiency virus infection. Clin Microbiol Rev 2004;17:729–759.
[9] Maródi L. Mucocutaneous Candidiasis. In: Sullivan KE, Stiehm RE, editors. Stiehm's immunodeficiencies. Amsterdam: Elsevier Inc; 2014. pp. 775–802.
[10] Mogensen TH. STAT3 and the Hyper-IgE syndrome: clinical presentation, genetic origin, pathogenesis, novel findings and remaining uncertainties. JAK-STAT 2013;2:e23435.
[11] Ouederni M, Sanal O, Ikinciogullari A, et al. Clinical features of Candidiasis in patients with inherited interleukin 12 receptor β1 deficiency. Clin Infect Dis 2014;58:204–213.
[12] Prando C, Samarina A, Bustamante J, et al. Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. Med (Baltimore) 2013;92:109–122.
[13] Meloni A, Willcox N, Meager A, et al. Autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. J Clin Endocrinol Metab 2012;97:1114–1124.
[14] Liu L, Okada S, Kong XF, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 2011;208:1635–1648.
[15] van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med 2011;365:54–61.
[16] Smeekens SP, Plantinga TS, van de Veerdonk FL, et al. STAT1 hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. PLoS One 2011;6:e29248.
[17] Tóth B, Méhes L, Taskó S, et al. Herpes in STAT1 mutation. The Lancet 2012;379:2500.
[18] Hori T, Ohnishi H, Teramoto T, et al. Autosomal-dominant chronic mucocutaneous candidiasis with STAT1-mutation can be complicated with chronic active hepatitis and hypothyroidism. J Clin Immunol 2012;32:1213–1220.
[19] Takezaki S, Yamada M, Kato M, et al. Chronic mucocutaneous candidiasis caused by a gain-of-function mutation in the STAT1 DNA-binding domain. J Immunol 2012;189:1521–1526.
[20] Tsumura M, Okada S, Sakai H, et al. Dominant-negative STAT1 SH2 domain mutations in unrelated patients with Mendelian susceptibility to mycobacterial disease. Hum Mutat 2012;33:1377–1387.
[21] Soltész B, Tóth B, Shabashova N, et al. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. J Med Genet 2013;50:567–578.
[22] Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 2011;332:65–68.
[23] Boisson B, Wang C, Pedergnana V, et al. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013;39:676–686.
[24] Naglik JR, Moyes DL, Wächtler B, Hube B. Candida albicans interactions with epithelial cells and mucosal immunity. Microbes Infect 2011;13:963–976.
[25] Kumamoto CA. Inflammation and gastrointestinal Candida colonization. Curr Opin Microbiol 2011;14:386–391.
[26] Gow NA, Hube B. Importance of the Candida albicans cell wall during commensalism and infection. Curr Opin Microbiol 2012;15:406–412.
[27] Vazquez JA, Sobel JD. Mucosal candidiasis. Infect Dis Clin North Am 2002;16:793–820.
[28] Hebecker B, Naglik JR, Hube B, Jacobsen ID. Pathogenicity mechanisms and host response during oral Candida albicans infections. Expert Rev Anti Infect Ther 2014;12:867–879.
[29] Zhu W, Filler SG. Interactions of Candida albicans with epithelial cells. Cell Microbiol 2010;12:273–282.
[30] Staab JF, Bradway SD, Fidel PL, Sundstrom P. Adhesive and mammalian transglutaminase substrate properties of Candida albicans Hwp1. Science 1999;283:1535–1538.
[31] Phan QT, Myers CL, Fu Y, et al. Als3 is a Candida albicans invasin that binds to cadherins and induces endocytosis by host cells. PLoS Biol 2007;5:e64.
[32] Gale CA, Bendel CM, McClellan M, et al. Linkage of adhesion, filamentous growth, and virulence

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in Candida albicans to a single gene, INT1. Science 1998;279:1355–1358.
[33] Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol 2009;27:485–517.
[34] Cypowyj S, Picard C, Maródi L, et al. Immunity to infection in IL-17-deficient mice and humans. Eur J Immunol 2012;42:2246–2254.
[35] Maródi L, Cypowyj S, Tóth B, et al. Molecular mechanisms of mucocutaneous immunity against Candida and Staphylococcus species. J Allergy Clin Immunol 2012;130:1019–1027.
[36] Puel A, Cypowyj S, Maródi L, et al. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 2012;12:616–622.
[37] Maródi L, Cypowyj S, Casanova JL, Puel A. The role of human IL-17 immunity in fungal disease. Curr Fungal Infect Rep 2013. DOI:10.1007/s12281-013-0131-4.
[38] Ness-Schwickerath KJ, Jin C, Morita CT. Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vgamma2Vdelta2 T cells. J Immunol 2010;184:7268–7280.
[39] Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol 2010;10:479–489.
[40] Aggarwal S, Gurney AL. IL-17: prototype member of an emerging cytokine family. J Leukoc Biol 2002;71:1–8.
[41] Netea MG, Maródi L. Innate immune mechanisms for recognition and uptake of Candida species. Trends Immunol 2010;31:346–353.
[42] Maródi L, Korchak HM, Johnston RB Jr. Mechanisms of host defense against Candida species. I. Phagocytosis by monocytes and monocyte-derived macrophages. J Immunol 1991;146:2783–2789.
[43] Maródi L, Schreiber S, Anderson DC, et al. Enhancement of macrophage candidacidal activity by interferon-gamma. Increased phagocytosis, killing, and calcium signal mediated by a decreased number of mannose receptors. J Clin Invest 1993;91:2596–2601.
[44] Dambuza IM, Brown GD. C-type lectins in immunity: recent developments. Curr Opin Immunol 2014;32C:21-27.
[45] Hernández-Santos N, Gaffen SL. Th17 cells in immunity to Candida albicans. Cell Host Microbe 2012;11:425–435.
[46] van de Veerdonk FL, Marijnissen RJ, Kullberg BJ, et al. The macrophage mannose receptor induces IL-17 in response to Candida albicans. Cell Host Microbe 2009;5:329–340.
[47] Bourgeois C, Majer O, Frohner IE, et al. Fungal attacks on mammalian hosts: pathogen elimination requires sensing and tasting. Curr Opin Microbiol 2010;13:401–408.
[48] Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of Candida albicans by the innate immune system. Nat Rev Microbiol 2008;6:67–78.
[49] Netea MG, Van Der Graaf CA, Vonk AG, et al. The role of toll-like receptor (TLR) 2 and TLR4 in the host defense against disseminated candidiasis. J Infect Dis 2002;185:1483–1489.
[50] Netea MG, Sutmuller R, Hermann C, et al. Toll-like receptor 2 suppresses immunity against Candida albicans through induction of IL-10 and regulatory T cells. J Immunol 2004;172:3712–3718.
[51] Martinez-Pomares L. The mannose receptor. J Leukoc Biol 2012;92:1177–1186.
[52] Heinsbroek SE, Taylor PR, Martinez FO, et al. Stage-specific sampling by pattern recognition receptors during Candida albicans phagocytosis. PLoS Pathog 2008;4:e1000218.
[53] Szolnoky G, Bata-Csörgö Z, Kenderessy AS, et al. A mannose-binding receptor is expressed on human keratinocytes and mediates killing of Candida albicans. J Invest Dermatol 2001;117:205–213.
[54] Bi L, Gojestani S, Wu W, et al. CARD9 mediates dectin-2-induced IkappaBalpha kinase ubiquitination leading to activation of NF-kappaB in response to stimulation by the hyphal form of Candida albicans. J Biol Chem 2010;285:25969–25977.
[55] Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727–1735.
[56] Lanternier F, Pathan S, Vincent QB, et al. Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med 2013;369:1704–1714.
[57] Wang X, Wang W, Lin Z, et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014;133:905–908.e3.
[58] Lanternier F, Barbati E, Meinzer U, et al. Inherited CARD9 deficiency in 2 unrelated patients with invasive exophiala infection. J Infect Dis 2014 DOI:10.1093/infdis/jiu412.
[59] Davis SD, Schaller J, Wedgwood RJ. Job's syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet 1966;1:1013–1015.
[60] Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. Immunol Rev 2005;203:244–250.
[61] Buckley RH. The hyper-IgE syndrome. Clin Rev Allergy Immunol 2001;20:139–154.
[62] Minengishi Y, Saito M, Tsuchiya A, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature 2007;448:1058–1062.

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[63] Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 2007;357:1608–1619.
[64] Jiao H, Tóth B, Erdos M, et al. Novel and recurrent STAT3 mutations in hyper-IgE syndrome patients from different ethnic groups. Mol Immunol 2008;46:202–206.
[65] Chandesris MO, Melki I, Natividad A, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. Medicine (Baltimore) 2012;91:e1–e19.
[66] Ma CS, Chew GY, Simpson N, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 2008;205:1551–1557.
[67] Milner JD, Brenchley JM, Laurence A, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 2008;452:773–776.
[68] Minegishi Y, Saito M, Nagasawa M, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med 2009;206:1291–1301.
[69] O'Shea JJ, Lahesmaa R, Vahedi G, et al. Genomic views of STAT function in $CD4^+$ T helper cell differentiation. Nat Rev Immunol 2011;11:239–250.
[70] O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med 2013;368:161–170.
[71] Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. Immunity 2012;36:515–528.
[72] Kane A, Deenick EK, Ma CS, et al. STAT3 is a central regulator of lymphocyte differentiation and function. Curr Opin Immunol 2014;28:49–57.
[73] Ma CS, Avery DT, Chan A, et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. Blood 2012;119:3997–4008.
[74] Siegel AM, Heimall J, Freeman AF, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. Immunity 2011;35:806–818.
[75] Conti HR, Baker O, Freeman AF, et al. New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome. Mucosal Immunol 2011;4:448–455.
[76] Tomalka J, Azodi E, Narra HP, et al. β-Defensin 1 Plays a Role in Acute Mucosal Defense against Candida albicans. J Immunol 2015 pii: 1203239 [Epub ahead of print]
[77] Boisson-Dupuis S, Kong XF, Okada S, et al. Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. Curr Opin Immunol 2012;24:364–378.
[78] Sampaio EP, Hsu AP, Pechacek J, et al. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. J Allergy Clin Immunol 2013;131:1624–1634.
[79] Kumar N, Hanks ME, Chandrasekaran P, et al. Gain-of-function signal transducer and activator of transcription 1 (STAT1) mutation-related primary immunodeficiency is associated with disseminated mucormycosis. J Allergy Clin Immunol 2014;134:236–239.
[80] Kilic SS, Puel A, Casanova JL. Orf Infection in a Patient with Stat1 Gain-of-Function. J Clin Immunol 2014 Nov 4. [Epub ahead of print]
[81] Lee PP, Mao H, Yang W, et al. Penicillium marneffei infection and impaired IFN-γ immunity in humans with autosomal-dominant gain-of-phosphorylation STAT1 mutations. J Allergy Clin Immunol 2014;133:894–896.
[82] Wang X, Lin Z, Gao L, et al. Exome sequencing reveals a signal transducer and activator of transcription 1 (STAT1) mutation in a child with recalcitrant cutaneous fusariosis. J Allergy Clin Immunol 2013; 131:1242–1243.
[83] Ives ML, Ma CS, Palendira U, et al. Signal transducer and activator of transcription 3 (STAT3) mutations underlying autosomal dominant hyper-IgE syndrome impair human CD8(+) T-cell memory formation and function. J Allergy Clin Immunol 2013;132:400–411.
[84] Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. Clin Infect Dis 2005;41:e38–e41.
[85] Vinh DC, Masannat F, Dzioba RB, et al. Refractory disseminated coccidioidomycosis and mycobacteriosis in interferon-gamma receptor 1 deficiency. Clin Infect Dis 2009;49:e62-65.
[86] Kobayashi M, Fitz L, Ryan M, et al. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. J Exp Med 1989;170:827–845.
[87] Stern AS, Podlaski FJ, Hulmes JD, et al. Purification to homogeneity and partial characterization of cytotoxic lymphocyte maturation factor from human B-lymphoblastoid cells. Proc Natl Acad Sci USA 1990;87:6808–6812.
[88] Trinchieri G. Interleukin-12: a cytokine at the interface of inflammation and immunity. Adv Immunol 1998;70:83-243.

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[89] Airoldi I, Guglielmino R, Carra G, et al. The interleukin-12 and interleukin-12 receptor system in normal and transformed human B lymphocytes. Haematologica 2002;87:434–442.
[90] Oppmann B, Lesley R, Blom B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000;13:715–725.
[91] Watford WT, Hissong BD, Bream JH, et al. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunol Rev 2004;202:139–156.
[92] McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. Immunity 2008;28:445–453.
[93] Filipe-Santos O, Bustamante J, Chapgier A, et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 2006;18:347–361. Erratum in: Semin Immunol 2007;19:136-137.
[94] Picard C, Fieschi C, Altare F, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am J Hum Genet 2002;70:336–348.
[95] Altare F, Lammas D, Revy P, et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and Salmonella enteritidis disseminated infection. J Clin Invest 1998;102:2035–2040.
[96] de Jong R, Altare F, Haagen IA, et al. Severe mycobacterial and Salmonella infections in interleukin-12 receptor-deficient patients. Science 1998;280:1435–1438.
[97] Altare F, Durandy A, Lammas D, et al. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 1998;280:1432–1435.
[98] Pedraza S, Lezana JL, Samarina A, et al. Clinical disease caused by Klebsiella in 2 unrelated patients with interleukin 12 receptor beta1 deficiency. Pediatrics 2010;126:e971–e976.
[99] Toy D, Kugler D, Wolfson M, et al. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. J Immunol 2006;177:36–39.
[100] Bulek K, Liu C, Swaidani S, et al. The inducible kinase IKKi is required for IL-17-dependent signaling associated with neutrophilia and pulmonary inflammation. Nat Immunol 2011;12:844–852.
[101] Chang SH, Dong C. Signaling of interleukin-17 family cytokines in immunity and inflammation. Cell Signal 2011;23:1069–1075.
[102] May MJ. IL-17R signaling: new players get in on the Act1. Nat Immunol 2011;12:813–815.
[103] Shen F, Gaffen SL. Structure-function relationships in the IL-17 receptor: implications for signal transduction and therapy. Cytokine 2008;41:92–104.
[104] Qian Y, Liu C, Hartupee J, Altuntas CZ, et al. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. Nat Immunol 2007;8:247–256.
[105] Novatchkova M, Leibbrandt A, Werzowa J, et al. The STIR-domain superfamily in signal transduction, development and immunity. Trends Biochem Sci 2003;28:226-229.
[106] Boisson B, Wang C, Pedergnana V, et al. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013;39:676–686.

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