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Genetic Susceptibility to Fungal Infections in Humans

Michail S. Lionakis, M.D., Sc.D.

Clinical Mycology Unit, Laboratory of Molecular Immunology, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland, USA

Abstract

Most fungal infections in humans occur in the setting of iatrogenic immunosuppression or HIV infection. In the absence of these factors, fungi cause mild, self-limited infections that typically involve mucocutaneous surfaces. Hence, when persistent or recurrent mucocutaneous infections (chronic mucocutaneous candidiasis [CMC]) or invasive fungal infections (IFIs) develop in a “normal” host, they are indicative of genetic defects causing innate or adaptive immune dysfunction. In this review, recent developments concerning genetic and immunologic factors that affect the risk for IFIs and CMC are critically discussed.

Keywords

Fungal infection; Genetics; Susceptibility; Immune dysfunction; Primary immunodeficiency; Chronic mucocutaneous candidiasis; Chronic granulomatous disease; Hyper-IgE syndrome; MonoMAC; Leukocyte adhesion deficiency; Severe combined immunodeficiency; Hyper-IgM syndrome; APECED; STAT1; STAT3; CARD9; DOCK8; Dectin-1; Toll-like receptors; IL-17; IL-12/IFN- γ axis

Introduction

Our understanding of genetic and immune perturbations that predispose to invasive fungal infections (IFIs) and chronic mucocutaneous candidiasis (CMC) has substantially advanced in recent years. With regard to IFIs, defects in phagocyte effector function due to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mutations predispose to infections by filamentous molds, and abnormalities in interleukin-12 (IL-12)/interferon- γ (IFN- γ) signaling predispose to infections by dimorphic fungi [1, 2]. These IFIs also occur in MonoMAC syndrome caused by *GATA2* mutations [3, 4]. *Pneumocystis* pneumonia (PCP) is seen in severe combined immunodeficiency (SCID) and hyper-IgM (HIGM) syndromes [5, 6]. Moreover, recent studies have shed light on allelic variations of immunomodulatory genes that seem to increase susceptibility to IFIs following hematopoietic stem cell transplantation (HSCT) [7, 8, 9•, 10, 11].

Furthermore, IL-17 signaling is critical for mucocutaneous anti-*Candida* host defense, and various correlates of IL-17 immunity are impaired in CMC caused by mutations in the autoimmune regulator (AIRE) gene, which causes the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome [12]; the Signal Transducer and Activator of Transcription-3 (*STAT3*) gene, associated with autosomal dominant hyper-IgE

Address correspondence and reprint requests to: Michail S. Lionakis, M. D., Sc. D., Building 10, Room 11N117, 9000 Rockville Pike, National Institutes of Health, Bethesda, MD 20892, Tel: 301-443-5089, Fax: 301-402-4369, lionakism@mail.nih.gov.

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syndrome (AD-HIES) [13]; the dedicator of cytokinesis-8 (*DOCK8*) gene, related to autosomal recessive (AR)-HIES [14•]; and *STAT1* [15•, 16•], Caspase recruitment domain-containing protein-9 (*CARD9*) [17•], IL-17 receptor-A (*IL-17RA*), IL-17 F [18•], and possibly dectin-1 [19•]. In this review, the genetic factors that predispose to the development of fungal disease are discussed independently for IFIs and CMC.

Genetic Susceptibility To Invasive Fungal Infections

Innate immunity protects against invasive infection by molds, dimorphic fungi, and yeasts. Hence, primary immunodeficiencies (PIDs) adversely affecting neutrophil function and monocyte/macrophage activation predispose to IFIs. Conversely, IFIs are not encountered in X-linked agammaglobulinemia, a humoral PID. Moreover, single nucleotide polymorphisms (SNPs) in innate immunity genes, primarily encoding pattern-recognition receptors (PRRs) and cytokines/chemokines, have been associated with increased susceptibility to invasive aspergillosis (IA) in recipients of allogeneic HSCT.

Invasive Fungal Infections in Primary Immunodeficiencies

Invasive Mold Infections

Phagocytes are critical for control of inhaled molds. Specifically, resident alveolar macrophages and recruited monocytes and neutrophils mediate conidial and hyphal killing through nonoxidative and oxidative cytotoxic mechanisms. Therefore, PIDs resulting in quantitative and/or qualitative defects in innate immune cells predispose to invasive mold infections (IMIs).

Chronic Granulomatous Disease—In the absence of iatrogenic factors, IMIs occur almost exclusively in chronic granulomatous disease (CGD), a rare PID (frequency, ~1/200,000) caused by mutations in the NADPH oxidase complex. Two thirds of CGD cases are caused by X-linked recessive defects in *CYBB* encoding the gp91-phox subunit of the NADPH oxidase, and one third are caused by autosomal recessive defects in *NCF-1*, *NCF-2*, and *CYBA* encoding subunits p47-phox, p67-phox, and p22-phox, respectively (reviewed in [1]). CGD phagocytes are defective in superoxide anion generation, resulting in attenuated oxygen-dependent microbiocidal activity via impaired K⁺ flux-mediated granule protease activation within phagocytic vacuoles [20]. NADPH-mediated neutrophil extracellular trap formation also contributes to fungicidal activity [21].

Invasive aspergillosis (IA) accounts for over one third of all infections in CGD [22] and typically occurs by age 20 in patients without underlying lung disease. In fact, inhalation of aerosolized decayed organic matter in mulch or hay may cause fulminant *Aspergillus* hypersensitivity pneumonitis (“mulch pneumonitis” [23]). *Aspergillus fumigatus* is the most common species but *Aspergillus nidulans* is uniquely seen in CGD, for reasons that have yet to be elucidated, and is distinctive because of its propensity to spread to adjacent structures and its inherent resistance to antifungal agents [24]. Less often, *Paecilomyces*, *Fusarium*, and *Scedosporium* are seen [22], whereas mucormycosis is uncommon and occurs only after corticosteroid use [25]. This fungus-specific difference in susceptibility to IA versus mucormycosis merits further investigation; it may relate to the greater phagocyte dependence on nonoxidative mechanisms for killing *Rhizopus* as opposed to *Aspergillus* [26]. In the past, IA was the leading cause of mortality in CGD, causing more than one third of all deaths, but the advent of potent triazoles has dramatically decreased IA-related mortality in recent years [22, 27].

Autosomal-Dominant Hyper-IgE Syndrome—Autosomal-dominant hyper-IgE syndrome (AD-HIES), caused by heterozygous dominant-negative mutations in the *STAT3*

DNA and SH2-binding domains [28], is characterized by staphylococcal skin abscesses, eczema, connective tissue defects, and elevated IgE [13]. The IMI susceptibility in AD-HIES is distinct from that of CGD, as AD-HIES phagocytes have normal effector function. IMIs in AD-HIES typically occur after age 30, exclusively in patients with anatomic lung defects secondary to prior bacterial pneumonias (e.g., bronchiectasis, pneumatoceles), which form a substrate for secondary mold colonization and infection [29]. About 28% of AD-HIES patients develop IFIs; IA is most common, followed by scedosporiosis. Despite therapy, IMI-related mortality approaches 20% [29].

MonoMAC—IA also occurs in the recently described syndrome of monocytopenia and susceptibility to mycobacteria, papillomaviruses, fungi, and myelodysplasia (MonoMAC) [3]. Both sporadic and autosomal dominant cases occur, the latter caused by missense *GATA2* mutations affecting the zinc finger-2 domain [4]. IFI incidence is 18–43%; that of IA is about 17%. The immunologic features of MonoMAC comprise profound circulating monocytopenia, B and NK lymphocytopenia, and decreased dendritic cells. Of interest, despite peripheral cytopenias, patients have macrophages and plasma cells at sites of inflammation. Neutrophils are variably affected, with abnormal granule content, dysplasia, and/or aberrant surface antigen expression [3]. Which of these defects is responsible for heightened IFI susceptibility in a subset of patients is unclear.

IMIs in Other Primary Immunodeficiencies—IMIs are occasionally encountered in autosomal recessive leukocyte adhesion deficiency type 1 (LAD-1), caused by mutations in *ITGB2* that encodes the $\beta 2$ -integrin common chain, leading to diminished granulocyte adhesion and migration [30]. Similarly, IMIs develop in LAD-1/variant syndrome, a distinct entity comprising a moderate LAD-1-like phenotype with a Glanzmann-like bleeding tendency [31]. An unexpectedly high incidence of IA (~30%) was reported in X-linked Wiskott-Aldrich syndrome (WAS) caused by *WAS* mutations [32]; although some cases were confounded by allogeneic HSCT, the incidence is still about three-fold higher than that in cancer patients after HSCT, suggesting a probable direct role of WAS protein in anti-*Aspergillus* immunity. Surprisingly, IMIs are infrequent in congenital neutropenia syndromes, with only a few cases reported in Kostmann syndrome, caused by *HAX1* mutations [33]. The rarity of IMIs in this setting likely relates to the short neutropenia duration (cyclic neutropenia by *ELA2* mutations [34]), the capacity for neutrophil mobilization after infection (WHIM syndrome by *CXCR4* truncations [35]), and the maintenance of circulating neutrophils over a critical threshold (*G6PC3* mutations [36]). Finally, IA has rarely been reported in apparently immunocompetent individuals [37], presenting an opportunity for deciphering novel genetic defects that confer risk of IMIs.

Invasive Infections by Dimorphic Fungi

IL-12/IFN- γ Pathway Defects—Macrophages are critical for controlling intracellular microorganisms, including mycobacteria and dimorphic fungi, by mediating antigen presentation, T-lymphocyte activation, cytokine production, and intracellular killing. Pathogen engulfment by macrophages results in production of IL-12p70, which stimulates T cells and NK cells through its receptor IL-12R, an IL-12 $\beta 1$ /IL-12 $\beta 2$ heterodimer, to secrete interferon (IFN)- γ . Then, IFN- γ acts through its receptor, an IFN- γ receptor 1 (IFN- γ R1) and IFN- γ R2 heterodimer, to activate STAT1, which translocates to the nucleus and upregulates the transcription of IFN- γ -related genes [2].

Mutations in the genes encoding IFN- γ R1, IFN- γ R2, IL-12R $\beta 1$, IL-12p40, and STAT1 cause Mendelian susceptibility to mycobacterial disease (MSMD, reviewed in [2]). The severity of the clinical phenotype in MSMD correlates with the magnitude of failure to produce or respond to IFN- γ . Hence, patients with AR complete loss of IFN- γ R1 or IFN-

γ R2 and AR STAT1 deficiency lack IFN- γ cellular responses and develop early-onset, life-threatening infections by nontuberculous mycobacteria, *Salmonella*, and in some instances, viruses. Conversely, less severe phenotypes are seen in AD partial IFN- γ R1 and IFN- γ R2 deficiencies, AD partial STAT1 deficiency, and AR lack of IL-12p40 or IL-12R β 1.

Disseminated and/or refractory infections by thermally dimorphic fungi also occur in some patients with MSMD. Thus, histoplasmosis and coccidioidomycosis were described in AD partial IFN- γ R1 deficiency due to a 4-bp deletion at base 818 (818del4) [38, 39], which exerts a dominant-negative effect on cellular responses to IFN- γ because of over-accumulation of mutant IFN- γ R1 receptors on the cell surface, which impede the function of normal receptors encoded by the wild-type allele. Moreover, IL-12R β 1 mutations have been described in patients with histoplasmosis (R521X), coccidioidomycosis (C186Y) and paracoccidioidomycosis (L77P) [40–42]. These mutations do not affect cellular responses to IFN- γ but result in abnormal IL-12-dependent and IL-23-dependent IFN- γ production, the latter because IL-12R β 1 is shared with the IL-23 receptor. To date, AR complete loss of IFN- γ R1 or IFN- γ R2, or IL12p40 mutations has not been associated with IFIs. Also, whether the absence of infections by the remaining pathogenic dimorphic fungi (*Blastomyces*, *Penicillium*, and *Sporothrix*) in MSMD reflects unique ecological niches of these fungi or underlies their differential dependence on the IL-12/IFN- γ axis for host defense remains to be determined.

Other Genetic Defects—Histoplasmosis is the most common IFI, together with IA, in MonoMAC [3]. It has also been reported in AD-HIES, common variable immunodeficiency, and X-linked HIGM syndrome [6, 29, 43]. Also, IL-4, IL-10 and TNF- α SNPs have been associated with paracoccidioidomycosis [44, 45], but additional studies are required to validate these preliminary findings.

Invasive Infections by Yeasts

Invasive Candidiasis—In stark contrast to the requirement for adaptive immunity for host defense against mucocutaneous candidiasis, innate immunity is critical in invasive candidiasis (IC). Not unexpectedly, IC is seen in CGD [22]. IC also occurs in myeloperoxidase (MPO) deficiency, the most common inherited phagocytic disorder (frequency: $\sim$ 1/2000) [46]. MPO catalyzes the production of hypochlorous acid during respiratory burst, and MPO-deficient phagocytes manifest impaired anti-*Candida* killing. However, the vast majority of MPO-deficient patients are asymptomatic, and IC occurs only in patients with AR-complete MPO deficiency and diabetes, thus a concomitant condition affecting neutrophil function [47]. Furthermore, three members of a consanguineous family with central nervous system IC were shown to have a homozygous point mutation in CARD9, resulting in a premature termination codon (Q295X) and impaired innate dectin-1 signaling [17•]. This is consistent with *CARD9* being an intracellular adapter molecule signaling downstream of dectin-1, and with the increased susceptibility to IC of *Dectin-1*^{−/−} and *Card9*^{−/−} mice [48, 49].

Cryptococcosis—Cryptococcosis has been described in MonoMAC, ADHIES, and HIGM syndromes, as well as in a patient with an IL-12R defect [3, 6, 29, 50], reflecting the importance of T lymphocytes and monocytes/macrophages in anticryptococcal immunity. Moreover, cryptococcosis is the most common opportunistic infection in idiopathic CD4 lymphocytopenia (ICL) [51], a rare, heterogeneous syndrome that likely encompasses patient cohorts with genetic defects yet to be discovered.

Trichosporonosis—Most *Trichosporon inkin* infections have been reported in CGD [52]. Because *T. inkin* is resistant to antifungals, favorable outcome typically requires surgical resection.

Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is common in SCID, a heterogeneous group of PIDs with combined cellular and humoral immunodeficiency resulting from T and NK lymphocytopenia and nonfunctional B cells. X-linked SCID, the most common form, is caused by *IL2RG* mutations, but there are also several AR forms due to mutations in *ADA*, *AK2*, *JAK3*, *IL7RA*, and other genes (reviewed in [5]). In contrast, PCP occurs less often in ICL [51].

PCP also develops in HIGM syndrome, a heterogeneous group of disorders characterized by hypogammaglobulinemia due to B-cell class switch recombination defects, with immunodeficiency caused by impaired T-lymphocyte and monocyte/macrophage effector function [6]. Specifically, PCP occurs in about 50% of patients with X-linked HIGM syndrome caused by mutations in CD40L, a key molecule for T-cell–monocyte/macrophage cross-talk [53]. PCP is also seen in the X-linked syndrome of anhidrotic ectodermal dysplasia with immunodeficiency, another form of HIGM syndrome caused by hypomorphic mutations in the nuclear factor- κ B (NF- κ B) essential modulator (*NEMO*) gene, which impair NF- κ B nuclear translocation [54]. Because of its high incidence, PCP prophylaxis should be administered to patients with SCID or HIGM syndrome.

Genetic Predisposition to Invasive Aspergillosis After HSCT

Approximately 10% of allogeneic HSCT recipients develop IA [7]. Although the risk of IA correlates with the degree of *Aspergillus* environmental exposure and the net state of immunosuppression, these factors alone do not fully explain why IA does not develop in the remaining 90% of patients. Hence, underlying genetic innate immune defects may influence the risk of IA; this premise applies for both HSCT donors and recipients, as inhaled *Aspergillus* interacts with recipient epithelial cells and donor myeloid cells.

On that basis, several studies have investigated the role of immune-related gene SNPs of HSCT donors and recipients in conferring risk for IA [7, 8, 9, 10, 11, 55–59]. These studies provide genetic associations that show promise for leading to better risk stratification of patients at greatest risk for IA, individualization of antifungal prophylaxis, and optimization of donor selection strategies. Yet they also have limitations. First, genetic associations may be biased by population stratification or confounded by different conditioning or chemotherapeutic regimens or antifungal prophylaxis practices in various oncology centers. It is also possible that the SNPs associated with IA may be in linkage disequilibrium with SNPs in other nearby genes, which are responsible for the observed phenotype. Last, SNPs may not be directly associated with IA but may affect other factors (such as cytomegalovirus [CMV] infection or graft-versus host disease) that influence the risk for IA. Therefore, careful population stratification, multivariate analysis of the outcomes, and validation studies using large patient cohorts are warranted. Moreover, as sequencing technologies continue to advance, future genome-wide association studies could provide significant information on genetic factors that predispose to IA following HSCT.

Toll-like Receptors

Toll-like receptors (TLRs) are a major family of PRRs, of which TLR2, TLR4, and TLR9 recognize fungal molecular motifs [60]. The most comprehensive study that examined the role of TLR allelic variations in affecting the risk of IA after HSCT found that a donor

haplotype (designated as “S4”) present in carriers of two *TLR4* SNPs in strong linkage disequilibrium (1063A/G and 1363 C/T) was associated with increased risk of developing IA in a screening patient cohort [7]. These SNPs impair TLR4 function; they cause hyporesponsiveness to inhaled lipopolysaccharide and have been associated with susceptibility to bacterial infections and IC [61, 62]. The association between the S4 haplotype in unrelated donors and risk of IA was then validated in a separate prospective cohort of 369 HSCT recipients [7]. In contrast, the S4 haplotype in HSCT recipients was not associated with IA, suggesting that TLR function in donor-derived myeloid cells is critical. Finally, the study showed that IA developed in only 1% of S4-negative/CMV-negative patients, compared with 22% of patients with S4 positivity with or without CMV infection. Moreover, the incidence of death not related to relapse was 22% among S4 negative/CMV-negative patients versus 35% in those positive for S4, CMV, or both. These data are remarkable, as they pave the way for future risk stratification studies in HSCT based on genetic factors.

In another study, the paired presence of *TLR4* 1063A>G and *IFN- γ* 874 T>A SNPs was found to further increase susceptibility to IA, compared with the *TLR4* SNP alone [55]. It is tempting to speculate that the concomitant presence of more than two SNPs may additively increase the risk profile for IA, but studies are needed to test this hypothesis. Moreover, the *TLR1* 239 G>C SNP or the presence of both *TLR1* 743A>G and *TLR6* 745 C>T SNPs in HSCT recipients, but not the donors, was associated with IA [8], suggesting that recipient alveolar epithelial TLR signaling plays a critical role. However, because macrophages are replaced by donor-derived cells several months after HSCT, the contribution of recipient alveolar macrophage TLR signaling cannot be ruled out. Finally, significant associations between the *TLR4* 1063A>G SNP and chronic cavity pulmonary aspergillosis (CCPA) and between the *TLR9* T-1237 C SNP and allergic bronchopulmonary aspergillosis (ABPA) have been reported in individuals who are not HSCT recipients, [63], indicating that TLRs are important in the pathogenesis of different forms of aspergillosis.

C-Type Lectins

Dectin-1 is a C-type lectin PRR that recognizes β -1,3-glucan [60]. A dectin-1 SNP (Y238X) leading to an early stop codon from loss of the last amino acids of the extracellular dectin-1 domain was found to cause decreased dectin-1 expression on immune cells, inability to bind β -glucan, and markedly decreased production of pro-inflammatory cytokines by leukocytes upon fungal stimulation [19].

The presence of the *DECTIN1* Y238X SNP in either donors or recipients of HSCT was shown to increase susceptibility to IA, with the greatest risk seen when the SNP was present in both donors and recipients [9•]. The requirement of intact dectin-1 in both hematopoietic and nonhematopoietic compartments for anti-*Aspergillus* immunity was further verified by generation of bone marrow chimeras in *dectin-1*^{-/-} mice [9]. Nonetheless, another study that examined IA patients with or without HSCT did not confirm the role of Y238X SNP in susceptibility to IA after HSCT [56]. Specifically, although the allelic frequency of the Y238X SNP was significantly higher in non-HSCT patients with IA (19%) than in HSCT recipients and healthy HSCT donors (~7%), the Y238X status in HSCT recipients or donors was not shown to influence IA risk. Likewise, the SNP was not associated with heightened risk of post-HSCT candidemia, although it appeared to be associated with increased *Candida* gastrointestinal colonization [57]. Thus, additional studies are required to resolve this discrepancy, which may relate to the small numbers and different patient populations that were studied.

Mannose-binding lectin (MBL) and surfactant protein A2 (SP-A2) are soluble C-type lectin PRRs, and MBL deficiency was more common in IA patients than in controls [64]; future

studies are required to investigate whether *MBL* SNPs that are known to influence MBL levels increase the risk of IA, as shown for CCPA and ABPA [65, 66]. *SP-A2* SNPs have also been associated with susceptibility to CCPA and ABPA [66], but their role in affecting the risk of invasive infection has not been defined.

Plasminogen

Haplotype-based computational genetic analysis of inbred mouse strains with differential susceptibility to IA revealed that plasminogen genetic variation correlated with survival [10]. A SNP was then identified in the human homolog (Asp472Asn), and it was shown that HSCT recipients homozygous or heterozygous for Asn472 were at increased risk of developing IA after HSCT, with an apparent gene-dosage effect [10]. This SNP could affect susceptibility to IA by impairing anti-*Aspergillus* immunity because plasminogen is a phagocyte chemoattractant and activator [67], or alternatively, by modulating host response to *Aspergillus*-induced tissue pathology. In particular, a SNP enhancing *Aspergillus*-plasminogen binding could trigger plasminogen activation, plasminogen-mediated extracellular matrix destruction, and could augment pathogen invasiveness as shown previously in group A *Streptococcus* [68].

Cytokines and Chemokines

SNPs in *CXCL10* (11 101 C/T, 1642 C/G, 908A/G) and *IFN- γ* (1101A/G) of HSCT recipients (but not donors) were associated with IA, with “CGAG” identified as the high-risk haplotype [11]. When exposed to *Aspergillus*, dendritic cells from patients with that haplotype showed markedly lower CXCL10 expression compared with wild-type genotype patients. In contrast, the *IL-10* 1082AA allele, which leads to low gene expression and protein levels, was associated with resistance to IA after HSCT [58]. Another study showed that the *IL-10* 1082*A/819*C/592*C haplotype was also associated with protection against IA [59]. Nevertheless, because IL-10 allelic variations influence the risk of graft-versus-host disease, these data should be interpreted with caution [69]. Finally, *TNFR1* SNPs, *IL-1* gene cluster SNPs (VNTR2/-889 C/-511 T haplotype), and a variable number of tandem repeats of *TNFR2* but not *TNFA* SNPs, were associated with increased susceptibility to IA in non-transplant cancer patients [70–72].

Genetic Susceptibility to Chronic Mucocutaneous Candidiasis

Contrary to phagocytes, T lymphocytes and epithelial cells are important for the control of mucocutaneous *Candida* infections. As such, mucosal candidiasis is common in acquired T-cell immunodeficiencies, including HIV infection. Less often, CMC develops because of inborn errors of immunity. Although most such cases are sporadic, they also cluster in families, transmitted in a Mendelian genetic manner. In recent years, human genetic studies have revealed the orchestrating role of IL-17 immunity in anti-*Candida* mucocutaneous host defense (Table 1) [15•, 16•, 17•, 18••, 19•, 73, 74••], consistent with data in animal models of mucosal candidiasis [75•].

Briefly, dectin-1-mediated *Candida* recognition by epithelial and myeloid cells leads to syk-CARD9-induced production of pro-inflammatory cytokines (IL-6, IL-23), which promote T-lymphocyte differentiation toward Th17 cells, a STAT3-dependent process [73]. Th17 cells secrete IL-17A, IL-17 F and IL-22, which then activate epithelial cells to produce neutrophil-recruiting chemokines and candidacidal antimicrobial peptides [76]. Several genetic perturbations along this pathway have been shown to cause CMC (Table 1) [12, 13, 14•, 15•, 16•, 17•, 18••, 19•]. Yet it is unclear whether the principal molecular cues that lead to CMC relate to defects at the epithelial level or at the leukocyte level, resulting in impaired epithelial activation, or both. In addition, the reasons why *Candida*-affected mucocutaneous

sites vary greatly in different CMC syndromes (Table 1) and even among CMC patients with the same genetic etiology are poorly understood. Importantly, because monoclonal antibodies against IL-17 and IL-12/23p40 are used in clinical trials of autoimmune diseases, it will be important to monitor these patients for the development of mucocutaneous candidiasis.

Hyper-IgE Syndrome

Approximately 80% of patients with autosomal dominant hyper-IgE syndrome (AD-HIES) develop CMC; dermatophytosis also occurs [13]. AD-HIES was the first syndrome in which impaired IL-17 immunity was implicated in CMC susceptibility. Specifically, CD4⁺ T lymphocytes from AD-HIES patients are unable to induce retinoid-related orphan receptor (ROR) γ t and differentiate into IL-17-producing T cells [73]. AD-HIES patients lack circulating IL-17-producing T cells, and their T cells produce less IL-17A and IL-22 after *Candida* stimulation, suggesting an intrinsic T-cell defect [73]. In addition, AD-HIES T cells fail to prime keratinocytes to produce β -defensins [74•], and AD-HIES patient saliva has diminished candidacidal activity associated with decreased histatin and β -defensin-2 levels [77].

Besides AD-HIES, there is a distinct AR-HIES entity in which patients lack the somatic features of AD-HIES, do not develop pneumatocoeles (nor IFIs), and are susceptible to cutaneous viral infections [78]. As in AD-HIES, CMC develops in about 80% of AR-HIES patients, and defects in T-lymphocyte IL-17 production have been demonstrated [79]. Unlike *STAT3* mutations, however, which impair initial steps in Th17 differentiation, AR-HIES patients appear to have defects in terminal Th17 differentiation events and/or Th17 cell persistence [79].

Mutations accounting for AR-HIES were recently described. Hence, a patient with AR-HIES, homozygous *TYK2* mutation, and mild CMC was described but IL-17 immunity parameters were not evaluated [80]. Instead, IL-12-induced Th1 differentiation was impaired, likely explaining the patient's susceptibility to mycobacteria, reminiscent of MSMD. Follow-up analysis of 15 AR-HIES families did not reveal any *TYK2* mutations [81]. Most recently, deletions and point mutations in the gene encoding DOCK8, an actin cytoskeleton regulator, were implicated in several AR-HIES kindreds [14•, 82]; the patients featured impaired T-cell activation and Th17 differentiation [82]. There are likely to be other genetic defects causing AR-HIES, which have not yet been defined.

APECED Syndrome

The autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome is a rare, autosomal recessive syndrome characterized by autoimmune endocrinopathies [83]. It is caused by mutations in autoimmune regulator (*AIRE*), a transcription factor that mediates thymic and peripheral self-reactive T-lymphocyte deletion [12]. CMC is the “signature” pathogen in APECED; it is the sole infectious disease phenotype and has 100% penetrance; the exception is Iranian Jews, fewer than 20% of whom develop CMC [84]. The unique Y85C mutation in these patients, compared with the most prevalent R257X mutation in other patient populations, suggests that different *AIRE* mutations may exert different effects on CMC susceptibility [12].

APECED patients have neutralizing autoantibodies against IL-17 F and IL-22, but not against other cytokines [85•, 86]. Of note, such autoantibodies were reported in thymoma patients who also develop CMC [85•, 87]. Therefore, B-cell-depleting anti-CD20 monoclonal antibody treatment may be effective in APECED, as previously shown in mice [88]. Actually, immunosuppression has been used to treat APECED patients, with

improvement of CMC [89]. Furthermore, peripheral blood mononuclear cells (PBMCs) in APECED patients have exhibited reduced IL-17 F and IL-22 secretion upon stimulation, implying that yet uncharacterized intrinsic leukocyte defects may also contribute to CMC [85•].

Dectin-1 Deficiency

A family with three siblings affected by chronic vulvovaginal candidiasis (CVC) and dermatophytosis was homozygous for the loss-of-expression and loss-of-function dectin-1 allele Y238X [19•]. The patients' PBMCs secreted less IL-17 than those of healthy controls, consistent with similar defects in *dectin-1*^{-/-} mice [90]. The syndrome appears dominant or co-dominant, as the heterozygous parents had a milder phenotype. Of note, the Y238X dectin-1 allele is a common SNP with a frequency of about 7% in Europe and up to 40% in the San population in South Africa. Because both homozygous and heterozygous patients had mild CMC and because CVC and onychomycosis are relatively frequent in the general population, a causal relationship between dectin-1 homozygosity or heterozygosity and these clinical phenotypes requires validation in population-based studies. In the meantime, it is premature to consider dectin-1 deficiency to be a *bona fide* PID.

CARD9 Mutations

Autosomal recessive CARD9 deficiency (Q295X) resulted in CMC and dermatophytosis together with IC in an Iranian family [17•]. The patients had decreased proportions of circulating IL-17⁺ T cells, suggesting a role of human CARD9 in Th17 differentiation, similar to what has been shown in mice [90]. The much greater severity of *Candida* infections seen in CARD9 deficiency than in patients with dectin-1 deficiency [19•] implies that *Candida* susceptibility in CARD9-deficient patients involves not dectin-1, but rather other CARD9-associated receptors like dectin-2, mincle (macrophage-inducible C-type lectin), or TREM1 (triggering receptor expressed on myeloid cells 1), or other receptors yet unknown.

STAT1 Mutations

Whole-exome sequencing in kindreds with autosomal dominant CMC found missense mutations in the STAT1 coiled-coil domain [15•, 16•]. The *STAT1* mutant alleles were gain-of-function by impairing nuclear dephosphorylation of activated STAT1, and led to increased STAT1-dependent cellular responses to IL-27, IFN- γ , and IFN- α/β , which potently inhibit Th17 development [15•]. As a result, patients with *STAT1* mutations had low proportions of circulating IL-17⁺ and IL-22⁺ T cells, and their PBMCs secreted very low amounts of IL-17A, IL-17 F, and IL-22 upon stimulation [15•, 16•]. Notably, these mutations differ from the autosomal recessive loss-of-function *STAT1* mutations underlying susceptibility to mucobacteria and viruses in MSMD, which are located in the coiled-coil, SH2, or DNA-binding domains and cause defective signaling of IFN- γ and IFN- α/β immunity [2]. Importantly, different germline mutations of the same gene may confer differential infection susceptibility via different cellular and molecular mechanisms. In fact, besides CMC, gain-of-function *STAT1* mutations in the coiled-coil and DNA binding domains caused by impaired dephosphorylation of STAT1 due to STAT1 hypomethylation appear to also predispose to invasive coccidioidomycosis (personal communication; Steven M. Holland, National Institutes of Health, 2011).

IL-17RA and IL-17 F Mutations

Direct genetic evidence for the role of IL-17 immunity in human susceptibility to CMC was recently demonstrated in two kindreds with CMC [18••]. In the first consanguineous Moroccan family, the cause of autosomal recessive CMC was complete deficiency in

IL-17RA, associated with lack of cellular responses of IL-17A and IL-17 F in leukocytes and fibroblasts. In the second kindred, the cause of autosomal dominant CMC was a hypomorphic dominant-negative *IL-17F* allele, which resulted in impairment of receptor binding and downstream bioactivity in leukocytes and fibroblasts.

Other Genetic Defects

CMC develops in T lymphocyte-associated PIDs including SCID, X-linked HIGM syndrome, ICL, and WAS [5, 6, 51]. CMC also develops in about 25% of patients with IL-12p40 and IL-12R β 1 deficiencies [40]; some of these patients have low proportions of T cells that produce IL-17 and IL-22, so they secrete low amounts of IL-17 and IL-22, likely because of impaired IL-23 responses [91]. Syndromes of CMC with genetic causes not yet defined include autosomal dominant CMC with hypothyroidism and autosomal dominant chronic isolated nail candidiasis [92, 93]. An association was described between CMC and the protein tyrosine phosphatase nonreceptor 22, 1858 T, a variant of the lymphoid protein tyrosine phosphatase R620W [94]. Also, the TLR3 L412F variant was associated with CMC susceptibility [95]. Nevertheless, it is improbable that TLRs directly contribute to CMC, as MyD88 and IRAK-4-deficient patients do not develop CMC [96]; in agreement, the TLR4 1063A>G SNP was not found to affect susceptibility to mucosal candidiasis [97]. Finally, MBL and IL-4 SNPs were shown to be associated with CVC [98, 99].

Conclusions

In recent years, a surge of studies has significantly advanced our understanding of genetic factors that modulate susceptibility to IFIs and CMC. Deciphering the genetic etiology of primary immunodeficiencies and the molecular and immunologic mechanisms that affect susceptibility to fungal disease may unravel novel targets for gene therapy. Moreover, identification of immune gene SNPs that confer heightened susceptibility to IFIs after allogeneic HSCT could enhance HSCT donor selection and facilitate individualized risk stratification strategies.

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Genetic perturbations associated with chronic mucocutaneous candidiasis (CMC): clinical and immunologic features

Table 1

Gene (chromosome)	Clinical syndrome (CMC incidence ^a)	Mode of inheritance	Site of <i>Candida</i> involvement	Other fungal infections	Nonfungal infection susceptibility	Noninfectious manifestations	IL-17 immunologic correlates of CMC susceptibility
<i>AIRE</i> (21q)	APECED (100% ^b)	AR	Oral mucosa, esophagus, vagina, skin, nails	None	None	<ul style="list-style-type: none">Autoimmune endocrinopathies (hypoparathyroidism and adrenal failure most common [$>80\%$], followed by hypogonadism [$\sim 60\%$]; diabetes, hypothyroidism and vitiligo are seen in $<20\%$ of patients)Oral/esophageal carcinomaDental enamel abnormalities	<ul style="list-style-type: none">Neutralizing anti-IL-17F and anti-IL-22 autoantibodiesImpaired IL-17F and IL-22 production by PBMCs upon stimulation
<i>STAT3</i> (17q)	HIES (80%)	AD	Oral mucosa, vagina, nails	<ul style="list-style-type: none">DermatophytesIMIs when lung defects (i.e., bronchiectasis or pneumatoceles) develop secondary to prior pneumoniasCryptococcosisHistoplasmosis	<ul style="list-style-type: none">Staphylococcal skin abscessesBacterial pneumonias	<ul style="list-style-type: none">Tooth development abnormalitiesDistinctive facial featuresEczemaBone fracturesScoliosis	<ul style="list-style-type: none">Impaired Th17 differentiation (early steps)Decreased proportions of circulating IL-17–producing T cellsImpaired IL-17A and IL-22 production by PBMCs upon stimulationDecreased levels of IL-17 induced candidacidal peptides in saliva
<i>DOCK8</i> (9p)	HIES (~80%)	AR	Oral mucosa, vagina, nails	None	<ul style="list-style-type: none">Staphylococcal skin abscessesBacterial/viral sinopulmonary infections	<ul style="list-style-type: none">Atopic eczemaCNS vasculitis	<ul style="list-style-type: none">Impaired Th17 differentiation (terminal steps)

Gene (chromosome)	Clinical syndrome (CMC incidence ^{d)}	Mode of inheritance	Site of <i>Candida</i> involvement	Other fungal infections	Nonfungal infection susceptibility	Noninfectious manifestations	IL-17 immunologic correlates of CMC susceptibility
<i>TYK2</i> (19p)	HIES-like, MSMD-like	AR	Oral mucosa	None	<ul style="list-style-type: none">Cutaneous viral infections (HSV, VZV, HPV, molluscum)Staphylococcal skin abscessesBacterial/viral sinopulmonary infectionsNontuberculous mycobacterial infections (BCG)SalmonellaViral infections (HSV, VZV, molluscum)	Eczema	ND
<i>CARD9</i> (9q)		AR	Oral mucosa, vagina	<ul style="list-style-type: none">DermatophytesInvasive candidiasis (meningitis)	None	None	<ul style="list-style-type: none">Decreased proportions of circulating IL-17–producing T cells
<i>DECTIN1</i> (12p)		AR	Vagina	Dermatophytes	None	None	<ul style="list-style-type: none">Impaired IL-17 production by PBMCs upon stimulation
<i>IL17RA</i> (22q)		AR	Oral mucosa, skin	None	<ul style="list-style-type: none">Staphylococcal skin infectionsSinopulmonary infections	<ul style="list-style-type: none">Atopic dermatitisAllergic rhinitis	Lack of cellular responses of IL-17A and IL-17F in leukocytes and fibroblasts
<i>IL17F</i> (6p)		AD	Oral mucosa	None	<ul style="list-style-type: none">Staphylococcal skin infectionsUpper respiratory infections	<ul style="list-style-type: none">Asthma	<ul style="list-style-type: none">Impaired binding of IL-17F to IL-17RADefective IL-17F bioactivity in leukocytes and fibroblasts
<i>STAT1</i> (2q)		AD	Oral mucosa, esophagus, vagina, skin, nails	PCP	<ul style="list-style-type: none">CMVBacterial infections	<ul style="list-style-type: none">HypothyroidismSquamous cell carcinoma	<ul style="list-style-type: none">Impaired IL-17A and IL-22 production by PBMCs upon stimulation

Gene (chromosome)	Clinical syndrome (CMC incidence ^a)	Mode of inheritance	Site of <i>Candida</i> involvement	Other fungal infections	Nonfungal infection susceptibility	Noninfectious manifestations	IL-17 immunologic correlates of CMC susceptibility
<i>IL12Rβ1</i> (19p)	MSMD (~25%)	AR	Oral mucosa	Histoplasmosis Coccidioidomycosis Paracoccidioidomycosis	<ul style="list-style-type: none">• Mycobacterial infections• Salmonella	None	ND
Various	SCID (~30–35%)	X-linked or AR	Oral mucosa	PCP			ND
CD40L (Xq)	HIGM syndrome (~5–10%)	X-linked	Oral mucosa, esophagus	PCP Cryptococcosis Histoplasmosis			ND
? (2p)		AD	Oral mucosa, skin, nails	Dermatophytes	None	<ul style="list-style-type: none">• Hypothyroidism• Squamous cell carcinoma	ND
? (11q)		AR	Nails	None	None	None	ND
<i>PTPN22</i> 1858C>T ^c (1p)		AR	Oral mucosa, skin, nails	None	Bacterial pneumonias	<ul style="list-style-type: none">• Endocrinopathies (hypothyroidism, adrenal failure, hypogonadism)• Bronchiectasis	ND
<i>TLR3</i> L412F ^c (4q)		AR	Oral mucosa, esophagus, skin, nails	None	<ul style="list-style-type: none">• Bacterial sinopulmonary infections• CMV	<ul style="list-style-type: none">• Endocrinopathies (hypothyroidism, adrenal failure, hypoparathyroidism, hypogonadism)• Bronchiectasis	ND

^aData on CMC incidence are presented for syndromes for which this information is available.

^bExcept for Iranian Jews with APECED, in whom CMC was described in 4 of 24 patients.

^cAllelic variants in this gene have been associated with CMC.

AD autosomal dominant; *APECED* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *AR* autosomal recessive; *BCCG* bacillus Calmette-Guérin; *CMV* cytomegalovirus; *CNS* central nervous system; *HIES* hyper-IgE syndrome; *HIGM* hyper-IgM; *HPV* human papillomavirus; *HSV* herpes simplex virus; *IMIs* invasive mold infections; *MSMD* Mendelian susceptibility to mycobacterial disease; *ND* not determined; *PBMCs* peripheral blood mononuclear cells; *PCP* *Pneumocystis* pneumonia; *SCID* severe combined immunodeficiency; *VZV* varicella zoster virus.