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Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals

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It has been estimated that there are at least 1.5 million fungal species, mostly present in the environment, but only a few of these fungi cause human disease. Most fungal diseases are self-healing and benign, but some are chronic or life-threatening. Acquired and inherited defects of immunity, including breaches of mucocutaneous barriers and circulating leukocyte deficiencies, account for most severe modern-day mycoses. Other types of infection typically accompany these fungal infections. More rarely, severe fungal diseases can strike otherwise healthy individuals. Historical reports of fungi causing chronic peripheral infections (e.g. affecting the nails, skin, hair), and invasive diseases (e.g. brain, lungs, liver), in otherwise healthy patients, can be traced back to the mid-20th century. These fungi typically cause endemic, but not epidemic diseases, are more likely to underlie sporadic than familial cases, and only threaten a small proportion of infected individuals. The basis of this 'idiosyncratic' susceptibility has long remained unexplained, but it has recently become apparent that 'idiopathic' fungal diseases, in children, teenagers, and even adults, may be caused by single-gene inborn errors of immunity. The study of these unusual primary immunodeficiencies (PIDs) has led to the identification of molecules and cells playing a crucial role in human host defenses against certain fungi at particular anatomic sites. A picture is emerging of inborn errors of IL-17 immunity selectively underlying chronic mucocutaneous candidiasis, with little inter-individual variability, and of inborn errors of CARD9 immunity underlying various life-threatening invasive fungal diseases, differing between patients.

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Introduction

Chronic or life-threatening fungal diseases typically occur in patients with overt immunodeficiencies (IDs), whether inherited or acquired [1,2]. They represent a major public health problem, with a growing population of patients at risk, due to increases in the frequency of invasive procedures, cancers, chemotherapy, and immunosuppressive treatments, and the aging of the population, together with the emergence of antifungal drug-resistant strains. These factors result in various types of breaches of the mucocutaneous barrier and deficiencies of circulating leukocytes. Fungal diseases are responsible for considerable morbidity and mortality worldwide [3,4]. Their pathogenesis remains poorly understood, because they frequently develop in patients with multiple morbidities, and, therefore, with several risk factors. For the same reason, these patients typically suffer from a number of other infections. However, in rare cases, severe fungal diseases can strike otherwise healthy patients with no known underlying risk factors [5]. These 'idiopathic' fungal diseases paradoxically provide us with a unique opportunity to gain insight into the general mechanisms of their pathogenesis.

It has recently become apparent that 'idiopathic' fungal diseases may be caused by single-gene inborn errors of immunity [6,7]. A first hint that this might be the case was provided by the observation that such diseases affect a very small minority of infected individuals, whereas the diseasing-causing fungi are ubiquitous in the environment [2,8]. Some well-characterized primary immunodeficiencies (PIDs), such as congenital neutropenia and chronic granulomatous diseases, underlie various infections, including relatively specific sets of fungal diseases

[9]. In addition, it is becoming increasingly clear that a number of viral and bacterial diseases striking otherwise healthy individuals result from single-gene inborn errors of immunity [10–13]. In this context, several fungal diseases, including chronic mucocutaneous candidiasis, *Candida* meningoencephalitis, deep dermatophytosis, and subcutaneous or invasive phaeohyphomycoses, have recently been shown to be caused by inborn errors of immunity [7,14,15].

The identification and characterization of genetic and immunological defects underlying fungal diseases can shed new light on the molecular and cellular mechanisms conferring protective immunity to specific fungi, by clarifying the pathogenesis of the corresponding fungal diseases in patients [16]. This work has important clinical implications, as it makes it possible to provide patients and their families with molecular genetic diagnoses and genetic counseling. Moreover, these advances pave the way for novel prophylactic or curative therapeutic interventions, both in the setting of these inherited IDs and in patients with these fungal diseases in the context of other, acquired IDs, based on a rational understanding of pathogenesis. Research into the human genetic basis of fungal diseases is important and timely, given the rapid emergence of antifungal drug-resistant strains and the high mortality rate associated with fungal diseases, despite appropriate antifungal treatment [2].

Chronic mucocutaneous candidiasis: inborn errors of IL-17 immunity

Chronic mucocutaneous candidiasis (CMC) is characterized by severe, persistent or recurrent infections of the mucosa, skin, and/or nails with *Candida* spp. CMC is common in patients with acquired or inherited profound T-cell immunodeficiency, who usually display multiple other, potentially more serious, infectious and/or autoimmune diseases [14]. CMC can also be syndromic in some PIDs without overt global T-cell deficiencies. These PIDs include autosomal dominant (AD, i.e. resulting from mono-allelic mutations) hyper-IgE syndrome (HIES) caused by dominant negative heterozygous *STAT3* loss-of-function (LOF) mutations, AD STAT1 gain-of-function (GOF), autosomal recessive (AR, i.e. resulting from bi-allelic mutations) autoimmune polyendocrinopathy syndrome type 1 (APS-1) caused by biallelic mutations of *AIRE*, and AR caspase recruitment domain-containing protein 9 (CARD9), IL-12 receptor β1 (IL-12Rβ1), IL-12p40 or RORγ/γT deficiencies [17]. These patients generally display fewer other infectious and/or autoimmune manifestations than patients with severe combined immunodeficiencies (SCID) or combined immunodeficiencies affecting T-cell numbers or functions, and CMC is one of the main clinical presentations. An analysis of the molecular and cellular basis of CMC in these PIDs has suggested a possible role of IL-17-mediated immunity in protection against mucocutaneous candidiasis [18]. Indeed, all these PIDs have CMC as a common clinical phenotype, and all are characterized by abnormally low proportions of circulating IL-17$^+$ T cells, or high serum levels of neutralizing autoantibodies against IL-17 cytokines (in the case of patients with AR APS-1). The low proportions of circulating IL-17$^+$ T cells result from impaired pro-Th17 cytokine signaling or production (e.g. AR IL-12p40 and IL-12Rβ1 deficiencies, impairing IL-23 production and response, respectively; AD STAT3 deficiency, impairing signaling downstream from IL-6, IL-23, and IL-21, in particular) [19]; the lack of a master transcription factor for IL-17$^+$ T cells and type 3 innate lymphoid cells (AR RORγT deficiency) [20]; an increase in signaling downstream from cytokines inhibiting IL-17$^+$ T-cell differentiation (e.g. AD STAT1 GOF that increases cellular responses to IFNs and IL-27, which inhibit Th17 cell differentiation) [21]; and the impaired production of pro-Th17 cytokines by phagocytes upon fungal recognition (AR CARD9 deficiency) [22••] (Figure 1). These studies have paved the way for the identification of inborn errors of immunity conferring CMC in otherwise healthy individuals [18].

Autosomal dominant IL-17F deficiency

AR IL-17RA deficiency, and AD IL-17F deficiency were identified (after the Sanger sequencing of candidate genes) in 2011, as the first genetic causes of isolated inherited CMC [23••]. The heterozygous missense mutation (S65L) of the *IL17F* gene was identified in five patients from an Argentinian multiplex family with early-onset CMC (within the first year of life), and two asymptomatic family members (indicating incomplete clinical penetrance) [23••]. The index patient was also reported to have had recurrent upper respiratory tract infections, asthma, and recurrent episodes of furunculosis since infancy. These patients had normal proportions of IL-17A- and IL-22-producing T cells, but it was not possible to evaluate the proportion of IL-17F-expressing T cells by flow cytometry, even for control cells [23••]. The S65L mutation did not affect the production of wild-type or mutant IL-17F monomers or homodimers or of IL-17A/IL-17F heterodimers. Instead, it affected the binding of the mutant S65L IL-17F protein to the IL-17RA/IL-17RC receptors expressed on the surface of control fibroblasts [23••]. Accordingly, control fibroblasts and keratinocytes displayed impaired responses to mutant IL-17F homodimers, and to wild-type IL-17A/mutant IL-17F and wild-type IL-17F/mutant IL-17F heterodimers [23••]. Heterodimers of the mutant IL-17F protein with either wild-type IL-17F or IL-17A exerted a dominant-negative effect on IL-17A- or wild-type IL-17F-mediated responses. The S65L IL-17F mutation is, therefore, a hypomorphic dominant-negative mutation [23••]. A heterozygous *IL17F* mutation was subsequently reported in a women and her son of Tunisian-German origin with early childhood onset of AD CMC, in the absence of any other infectious phenotype, including staphylococcal disease in particular [24]. This mutation has not yet been characterized, but corresponds to the second case of AD IL-17F deficiency. These