Human Invasive Mycoses: Immunogenetics on the Rise

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(See the major article by Lanternier et al on pages 1241–50.)

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Exophiala species are ubiquitous dematiaceous yeast-like fungi of the order Chaetothyriales that bear melanin-like pigment in their cell wall that is responsible for their dark color and is thought to be a major fungal virulence factor \([1–3]\). Among the agents of phaeohyphomycosis (cutaneous, subcutaneous, and invasive infections caused by dark-walled fungi), most human Exophiala infections are subacute to chronic and confined to the skin, typically following traumatic inoculation \([1–3]\). Invasive Exophiala infections are rare and associated with high fatality rates \([1–3]\). Exophiala dermatitidis accounts for most of these invasive infections and has a tropism for the central nervous system; Exophiala spinifera infection is less common, with no neurotropism but with a predilection for bone \([1–3]\). Until now, inherited susceptibility to invasive Exophiala infection was recognized only in patients with chronic granulomatous disease (CGD) \([4]\), who have defects in phagocyte oxidative cytotoxicity \([5, 6]\).

In this issue of The Journal of Infectious Diseases, Lanternier et al describe 2 patients with autosomal recessive CARD9 deficiency who developed disseminated Exophiala infections \([7]\): an Angolan girl who presented at 5 years of age with E. dermatitidis infection of the brain and liver and an Iranian woman who presented at 18 years of age with E. spinifera infection of the subcutaneous tissue, bone, and lung. These cases identify CARD9 deficiency as a critical genetic risk factor for invasive Exophiala infection in humans, further expanding the spectrum of human invasive fungal disease associated with CARD9 deficiency. Other CARD9-associated infections include those caused by Candida, Trichophyton, and Phialophora species \([8–11]\). Therefore, CARD9 mutations are likely to account for some of the invasive phaeohyphomycosis infections in putatively immunocompetent patients, particularly those caused by neurotrophic fungi such as Cladophialophora, Fonsecaea, Rhinocladiella, Curvularia, Exserohilum, and Chaetomium species \([1–3]\).

CARD9 is a key adaptor molecule that complexes with MALT1 and BCL-10 to relay syk-mediated fungal recognition signals \([12, 13]\). Fungal sensing occurs through several immunoreceptor tyrosine-based activation motif–associated C-type lectin receptors (CLRs), including dectin-1, dectin-2, dectin-3, mincle, and, likely, others yet undiscovered \([14–17]\). This central positioning of CARD9 downstream of multiple fungal sensors likely accounts for the diverse spectrum of invasive fungal infections in patients with loss-of-function CARD9 mutations. The occurrence of spontaneous invasive fungal infections in patients with CARD9 deficiency and the absence of similar infections in patients with MYD88 or IRAK4 mutations underscore the critical differences between the human C-type lectin and Toll-like receptor pathways \([7–11, 18]\).

Intriguingly, there is, so far, no correlation between specific CARD9 mutations and specific invasive fungal infections; also, all CARD9-deficient patients with invasive fungal infections have been infected by only a single fungal pathogen \([7–11]\). Further, no pulmonary invasive fungal infections have yet been reported in CARD9-deficient patients, despite the ubiquity of inhaled filamentous fungi. Presumably, CARD9 will have critical functional roles in the induction of fungus-, CLR-, anatomical site–, and cell type–specific protective immune responses \([19]\). In addition, it remains puzzling that some CARD9-deficient patients present with invasive fungal disease early in life, whereas others exhibit adult-onset disease \([7–11]\).

The mechanisms by which CARD9 deficiency predispose to invasive fungal infections remain elusive but are likely to be somewhat distinct from those that account for enhanced susceptibility to chronic mucocutaneous candidiasis (CMC),
also encountered in some CARD9-deficient patients. The array of human monogenic disorders with impaired interleukin 17 (IL-17) immunity, either directly (ie, mutations in IL-17RA, IL-17F, and ACTI) or indirectly (ie, mutations in STAT1, STAT3, AIRE, Dock8, IRF8, and STK4), has shed light on the critical role of IL-17 signaling in mucosal but not systemic anti-Candida host defense [6, 20]. Although CARD9-deficient patients with CMC have been reported with impaired T-helper type 17 (Th17)—dependent immune responses [8], those with invasive fungal disease, such as a patient in the report by Lanternier et al [7], produce IL-17 adequately upon T-lymphocyte stimulation, indicating that low peripheral blood Th17 levels are neither necessary nor sufficient for invasive fungal infections.

The profound defects displayed by patient mononuclear cells in induction of proinflammatory cytokines, such as interleukin 1β, interleukin 6, and tumor necrosis factor α [8–11], which are indispensable for orchestrating effective innate antifungal immune responses [17], likely play a significant role in invasive fungal disease susceptibility in CARD9 deficiency. Decreased killing of unopsonized Candida by CARD9-deficient neutrophils is a potential mechanism contributing to impaired pathogen control in the central nervous system, where serum protein opsonization may be suboptimal [9]. Recent work has elegantly defined the CARD9-dependent pathway in human neutrophils for nonoxidative killing of unopsonized Candida, which incorporates complement receptor 3 and phosphatidylinositol 3-kinase signaling [21]. Unlike the case for Candida, killing of Aspergillus appears to be CARD9 independent [9]. However, much more work is necessary to determine the full scope of the impaired neutrophil responses accounting for fungus-specific susceptibility in CARD9 deficiency. Besides neutrophils, tissue-resident and recruited mononuclear phagocytes play critical roles in innate host defense against fungal invasion [22, 23] and are incompletely defined in CARD9 deficiency.

What is the therapeutic importance of diagnosing CARD9 deficiency? A patient with persistent refractory Candida meningoencephalitis in the setting of CARD9 deficiency was successfully treated with adjuvant granulocyte macrophage colony-stimulating factor (GM-CSF) [24]. GM-CSF exerts pleiotropic effects on innate immune responses, including enhancing human neutrophil candidacidal activity [25]. However, its precise mechanism of action in CARD9 deficiency, whether augmenting neutrophil effector function, monocyte/macrophage function, or even lymphoid responses, is unclear. The possible role of GM-CSF adjunctive therapy in disseminated Exophiala and other fungal infections in CARD9 deficiency, especially given their poor prognosis with conventional antifungal therapy, will also be essential to determine [1–3].

Besides CARD9, the report by Lanternier et al [7] highlights the explosion that we have witnessed in the identification and characterization of genetic disorders that predispose to invasive fungal disease over the past decade. Before that, only CGD, caused by mutations in any of the 5 subunits of nicotinamide adenine dinucleotide phosphate oxidase, and complete myeloperoxidase (MPO) deficiency, both disorders of the phagocyte oxidative machinery, were known to lead to inherited susceptibility to invasive mycoses [5, 6]. Of note, the spectrum of fungal disease differs substantially between CGD and MPO deficiency. Invasive candidiasis, but no other fungal infection, occurs in a small proportion of patients with complete MPO deficiency, whereas CGD is the leading cause of pulmonary infections by Aspergillus and other inhaled molds in the absence of iatrogenic risk factors. Invasive candidiasis occurs infrequently in CGD, and there are no infections by dimorphic fungi [5].

On the other hand, severe disseminated and/or refractory infections by endemic dimorphic fungi, such as Histoplasma, Coccidioides, and Paracoccidioides species, are seen in patients with mutations in the interleukin 12 (IL-12)/interferon γ (IFN-γ) pathway, which is crucial for control of intracellular pathogens [6]. IL-12 production by activated macrophages stimulates T lymphocytes and natural killer (NK) cells to secrete IFN-γ, which then acts on macrophage IFN-γ receptors to activate STAT1, which, in turn, translocates to the nucleus and upregulates the transcription of IFN-γ–related genes, leading to fungal clearance [6].

Tachyphylaxis to IFN-γ–dependent immunity has been implicated in susceptibility to disseminated histoplasmosis and coccidioidomycosis in patients with gain-of-function mutations in the DNA-binding and coiled-coil domains of STAT1 [26]. Some patients with gain-of-function STAT1 mutations also develop CMC, as well as invasive mold infections, for unclear reasons [6, 27–29]. Strikingly, mycobacterial but not fungal infections are seen in patients with loss-of-function STAT1 mutations [6]. Thus, much more work is required to define the overlapping and separate functional roles of STAT1 in fungal and mycobacterial immunity.

In addition to the interrelated members of the IL-12/IFN-γ pathway, the transcription factor GATA2 mediates systemic but not mucosal antifungal host defense. About 30% of patients with GATA2 mutations develop invasive fungal disease caused by molds, endemic dimorphic fungi, and Cryptococcus but not by Candida [30]. GATA2 has pleiotropic effects in cells of the myeloid and lymphoid lineage; deficiency causes B and NK-cell cytopenia, as well as peripheral monocytopenia and lack of circulating and tissue-resident dendritic cells. There are also variable granulocyte abnormalities that may account for their enhanced fungal infection susceptibility [30]. Patients with autosomal-dominant hyper–immunoglobulin E syndrome due to dominant-negative mutations in the transcription factor STAT3 also develop CMC, and in the setting of bronchiectasis, approximately 20% of patients also develop pulmonary mold disease [6, 31]. Recurrent bacterial pneumonias result in bronchiectasis and pneumatoceles,
which can then become colonized by inhaled molds, allowing for subsequent fungal invasion [31]. Thus, the susceptibility to invasive molds in STAT3 deficiency seems to depend on underlying structural lung disease, apparently making it separate from susceptibility to CMC.

In summary, the report of Lantener et al [7] broadens the spectrum of invasive fungal infections that are associated with inborn errors of immunity. The fact that these defects can be so limited in scope and so late in onset suggests that other such defects may be found and should be sought in individuals who were previously thought to be immunocompetent. The diagnosis of invasive fungal infections in patients without obvious underlying risk factors (immunosuppression, lymphoma, transplantation, and steroid use) should trigger a targeted genetic and immunological evaluation to determine possible underlying causes for opportunistic infection. To become invasive, molds, yeasts, and dimorphic fungi must exploit narrow but critical deficits in immunologic and structural host defense. The fact that these defects can be focal, can appear late, and can be apparently limited to only a few species of microbes means that we must all now become geneticists.

Notes

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