Perspective

Genetic susceptibility to Candida infection: a new look at an old entity

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The identification of the first molecular defect leading to Mendelian Susceptibility to Mycobacterial Disease (MSMD),[1] a rare syndrome conferring predisposition to disease caused by weakly virulent mycobacteria (such as Mycobacterium bovis, Bacille Calmette Guérin vaccines and environmental mycobacteria), has led to a paradigm shift in the field of primary immunodeficiencies in the last two decades. The "classic" patient with multiple immunologic abnormalities, conferring a broad susceptibility to multiple and recurrent infectious diseases caused by both weakly pathogenic and more virulent microorganisms, was the main Primary Immunodeficiency (PID) phenotype identified. Since 1996, mutations causing MSMD have been found in at least 6 genes related to interferon (IFN)-γ-mediated immunity.[2] Intriguingly, this has opened the door to the identification of a molecular pathogenesis in patients affected by a narrow to extremely narrow susceptibility to bacterial, viral and fungal infections.[3-7] These patients, more common than originally thought, are often otherwise healthy and are not prone to other unusually severe infections.

CANDIDA SPECIES INFECTION AND CHRONIC MUCOCUTANEOUS CANDIDIASIS (CMC)

The genetic susceptibility to infections due mainly to Candida species is a rare condition which may exist as a PID, potentially associated to a general immune dysregulation or to organ-specific syndromes (e.g. thyroid disease). CMC is the PID defined as persistent or recurrent infection of the skin, nails and mucous membranes, most commonly caused by *Candida albicans*, that can be related to a variety of disparate genetic defects, of which many have only recently been characterized. Although different underlying diseases predispose to *Candida spp.* infection of oral, gastrointestinal and cutaneous tissues, they may be associated with primary or secondary immunodeficiencies. Regarding secondary causes, HIV infection is common, although many other etiologies are known and must be considered in differential diagnosis.[8] Diabetes mellitus, denture stomatitis, iron deficiency, oral and inhaled corticosteroid treatment, HIV infection and immunosuppressive or antibiotic treatments are listed among the clinical factors which may finally lead to modifications of oral, gastrointestinal and cutaneous microbiomes. These factors enhance the susceptibility to infection by *Candida spp.,* mainly through impairment of immunity to fungi or of epithelial structure and function, that may result in transient, episodic mucocutaneous candidiasis or in a chronic course of fungal infection. Similarly, the patients affected by genetic forms of CMC (Figure 1) have, usually since infancy, recurrent bouts or chronic infection by Candida of tongue, oral cavity, skin and genitals (Figure 2A and 2B), but rarely develop

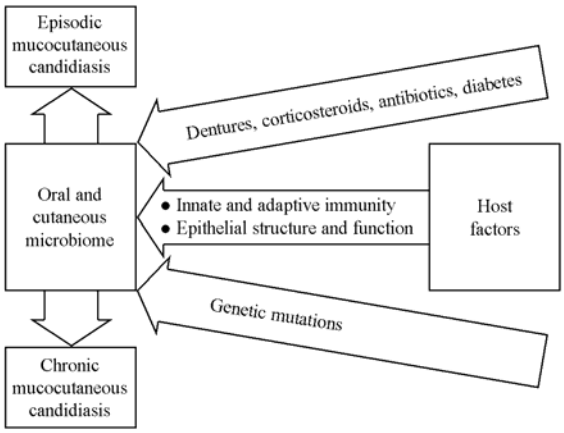

Figure 1. The normal mucocutaneous microbiome of healthy subjects largely depends from its relationship with host factors; it can be transiently modified by many factors, more often predisposing to acute Candida infection. Genetic causes may at the same time contribute to a permanent impairment of host defences resulting in chronic, unresolving mucocutaneos infections.

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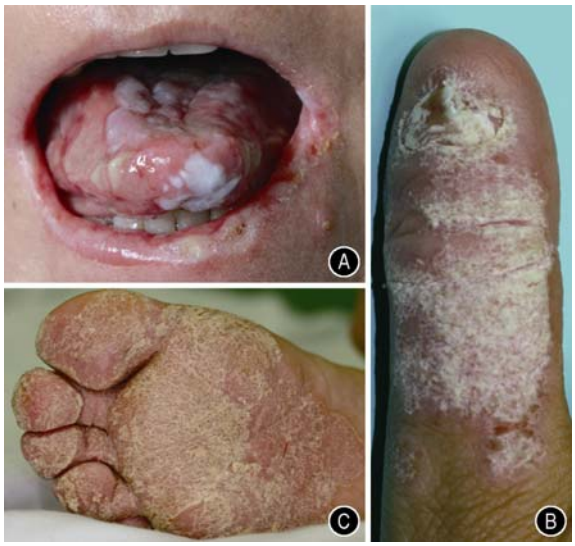

Figure 2. Clinical presentation of *C. albicans* infection in a CMC patient: whitish and yellowish plaques on the tongue and perleche **(A)**, skin and nail of the thumb **(B)**, skin of the foot **(C)**, showing chronic diffuse candidiasis.

systemic fungal infection or candidiasis of parenchymal organs.[9,10] Long-standing or resistant infection by Candida may show the debilitating features of chronic diffuse candidiasis (Figure 2C) or the formation of granulomas.[8] A severe, often disfiguring, history of cutaneous infections by Dermatophytes is another relevant feature seen in CMC patients.[11,12] Among the inherited forms of CMC disease sporadic, autosomal dominant (MIM 114580) and autosomal recessive (MIM 212050) forms have been described.[11] Moreover, similar clinical patterns of candidiasis may be shared by other PIDs, mainly Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; also called APS-1; MIM 240300), IL-12 receptor beta-1 deficiency[13] (MIM 601604) and autosomal dominant or recessive hyper-IgE syndrome (MIM 147060 and 243700).[14] Very recently, several studies have shed light on the pathogenesis of genetically determined forms of candidiasis, which had been elusive for a long time.

MONOGENETIC CAUSES OF CMC

CARD9 and Dectin-1 deficiencies

Animal models have suggested that a multipart pathway, starting from the yeast transmembrane pattern recognition receptor Dectin-1 (or alternatively from TLRs, Dectin-2, DC-SIGN, mincle) on epithelial cells and phagocytes, leads to the activation of the CARD9 signaling complex that leads to the activation of NF-κB and mitogen-activated protein kinases (MAPKs).[15] These pathways in turn produce cytokines involved in differentiation of CD4+ T-lymphocytes toward the Th17 phenotype, crucial for adaptive antifungal immunity.[16,17] In 2009, The first monogenetic defects in humans were reported in patients with the clinical features of CMC and other mycoses,[18,19] caused by mutations in the genes encoding respectively for CARD9 and Dectin-1, providing new insights on the relevance of innate immunity in precisely controlling fungal infections. These defects, resulting in phenotypes of CMC and dermatophyte infections which differ in clinical severity, are linked to the role these proteins play in the induction of multifaceted Th17 lymphocytes[20] and their production of interleukins (e.g. IL-17 and IL-22) for host defense against fungi, mainly at epithelia and mucosal sites.[21,22]

Interleukin (IL)-17F and IL-17RA mutations

The possible role for IL-17 in defense against *Candida albicans in vivo* was showed by Eyerich and colleagues[23] in patients with isolated CMC and reduced levels of Th 17 responses. Heterozygous mutations (dominant-negative) in the cytokine IL-17F were shown by Puel et al[24] to result in reduced IL-17F biological activity in a family with CMC, as well as in another CMC family a homozygous mutation in the IL-17 receptor A (IL-17RA) resulted in abrogated IL17-F and IL-17A/F heterodimers signaling. These findings again underscore the key role of IL-17 cytokine family in immune responses elicited by fungi at epithelial sites of infection, by linking lymphoid to myeloid and epithelial defense mechanisms.[25,26]

STAT1 mutations

Two groups revealed as another genetic cause, accounting for most of the sporadic and hereditary autosomal dominant CMC cases, the presence of heterozygous STAT1 mutations,[27,28] a gene already noted in the past for causing MSMD[7] and susceptibility to viral infections.[29] These newly described activating mutations of the coiled-coil domain of STAT1, through hyper-phosphorylation and impaired IL12R/IL23R signaling,[24,30] impair the STAT3-mediated Th17-responses and increase responsiveness to interferon (IFN)-γ. Stronger cellular responses to IFN-α/β have been also documented, and remarkably might account for the well known presence of thyroid autoimmunity and systemic lupus erythematosus in these patients. Impaired immunity to cytomegalovirus (CMV), autoantibody elevation or autoimmune endocrine diseases are other commonly observed features,[31-34] yet to be fully explained.

Toll-like receptor 3 (TLR3) mutations

TLRs play a first-line role for sensing pathogens, mediating response to several fungal species, including Candida.[35] Another syndrome characterized by non-invasive CMC, CMV infection, and autoimmunity has been described to be associated with the mutation L412F in the TLR3, affecting a highly conserved aminoacid residue.[36] Clinical features also include autoimmune pancytopenia, lung disease, arthritis and vitiligo. Altered interferon γ and λ production and low NF-κB activation upon TLR3 stimulation have been demonstrated.[37] Mutations in Dectin-1, CARD9, autoimmune regulator (AIRE) or TLR1, TLR2, TLR4, TLR6 were also excluded. Its relationship with STAT1, IL-17F or IL-17RA mutations has not been reported.

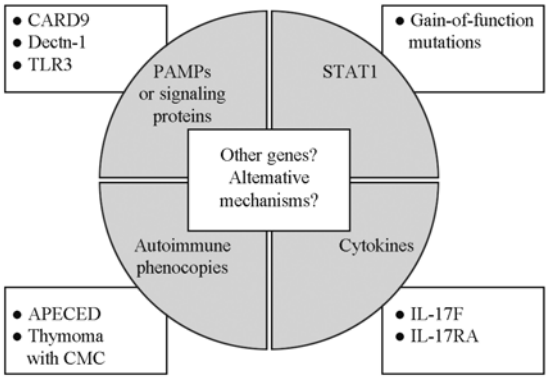

Figure 3. Summary of the diseases which share non-invasive CMC as their main clinical phenotype.

CMC IN APECED

Impairment of the Th17 lymphocytes and/or their cytokines appears to be the common denominator of heterogeneous but clinically related disorders. New evidence supporting the role of IL-22 in protection from candidiasis has also been reported.[38] APECED is a rare autosomal recessive disease due to mutations in the AIRE gene, whose role is essential for presenting antigens to T cells in the thymus, facilitating negative selection. As a consequence of its defect, patients with APECED suffer from multi-organ autoimmunity.[39] The mechanism responsible for development of CMC in the course of this disease has been elusive for a long time, even though previous work pointed to a possible autoimmune basis. Finally, the discovery in humans of neutralizing autoantibodies against IL-17A, IL-17F and IL-22, has been demonstrated in APECED.[40] The same autoantibodies has been shown also in CMC occurring in the course of thymoma.[40] The basis of CMC in these diseases again strongly supports the pivotal role of IL-17 and IL-22 producing cells in host defense against Candida, in particular at mucosal sites.

CONCLUSION

Taking together the recent reports on the causes of inborn Mendelian susceptibility to Candida infection and their "autoimmune phenocopies", the evidence indicates that in humans IL-17A, IL-17F and IL-22 are essential drivers for protective immunity to *C. Albicans in vivo*. In humans, mutations in STAT1 underlie susceptibility to three different types of infectious disease (MSMD, viral diseases and CMC), also leading to coexistence of autoimmune dysregulation. The CMC in the context of patients bearing AIRE mutations can be seen as a phenocopy of immunodeficiencies that impair the Th17 circuit, mediated by autoimmunity to cytokines. Additionally, other genes or novel mutations involved in the pathogenesis of CMC via regulation of immune response or via alternative, undisclosed mechanisms, will be probably discovered in the near future (Figure 3). As already been pointed out,[2] the novel phenotypes of immunodeficiency offer unique "experiment of nature" for understanding the complexity of immune mechanisms and functions.

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