Basic Genetics and Immunology of Candida Infections

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KEYWORDS

• *Candida* • Candidiasis • Genetics • Immunology

KEY POINTS

- Genetic factors play a critical role in the pathogenesis of both mucocutaneous and invasive candida infections.
- Monogenic disorders that impair Th17 deficiency cause chronic mucocutaneous candidiasis.
- Monogenic disorders that are linked to neutrophil deficiencies predispose patients to invasive candidiasis.
- Polymorphisms in genes from the type I interferon pathway increase susceptibility to systemic candidiasis.

INTRODUCTION

Candida species are a genus of yeasts that, under normal circumstances, are nonpathogenic commensal microorganisms in humans. However, they are the predominant opportunistic fungal pathogens, and cause superficial and invasive infection in immunocompromised individuals that is associated with significant morbidity and mortality. Risk factors for candida infections include immunosuppressive therapy, mucosal damage, the presence of indwelling catheters, and prolonged hospitalization.[1] However, mucocutaneous or systemic candidiasis often cannot be explained by just these risk factors, and not all individuals with these risk factors develop candida infections. Therefore, it is thought that genetic factors in addition to these risk factors must play a critical role in the pathogenesis of candida infections.

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With the development of novel human genetic screening tools, the contribution of genetic factors in the susceptibility to both mucocutaneous and invasive candidiasis has been extensively studied. This work has led to novel insights in the genetic and molecular pathogenesis of candida infections. Among those studies, several genes that impair antifungal immunity have been found to predispose to chronic mucocutaneous candidiasis (CMC) and invasive candidiasis. Meanwhile, common polymorphisms in genes involved in antifungal immunity have also been linked to different types of candida infection, such as recurrent vulvovaginal candidiasis (RVVC) and candidemia. This article summarizes recent findings concerning the genetics and immunology of candida infections, which not only have added to the current understanding of fungal immunology but will also help clinicians to design novel immunotherapeutic approaches.

MONOGENIC INHERITANCE OF CANDIDA INFECTIONS

As its name implies, CMC is characterized by recurrent or persistent infections of the skin, nails, and mucosal membranes with *Candida* species, mainly *Candida albicans*.[2] CMC may present as a distinct clinical entity, in which it is the only or principal manifestation (known as isolated CMC or CMC disease). It may also present as one of the key manifestations of a syndrome in children with primary immunodeficiency (PID) diseases (known as syndromic CMC). CMC can also be observed in addition to increased susceptibility to other infections in patients with acquired or inherited immunodeficiencies.[3] An overview of monogenetic disorders of candida infections is given in **Table 1** and **Fig. 1**.

Isolated Chronic Mucocutaneous Candidiasis

In 2009, autosomal recessive (AR) caspase recruitment domain–containing protein 9 (*CARD9*) deficiencies were discovered to cause isolated CMC.[4] CARD9 is a key adaptor molecule expressed in myeloid cells downstream of the pattern recognition receptors (PRRs) that recognize fungal cell wall components and subsequently activate spleen tyrosine kinase (Syk).[5] After phosphorylation, CARD9 binds B-cell lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) to form the CBM complex, resulting in nuclear factor kappa B (NF-κB) activation and innate antifungal immunity, thereby triggering the differentiation of naive T cells into T-helper (Th) 17 cells.[6] *CARD9*-deficient patients show reduced tumor necrosis factor (TNF)-α production and circulating interleukin (IL)-17–producing T cells,[4] underscoring the importance of CARD9-dependent pattern recognition signaling in mucocutaneous antifungal host defense.

In 2011, heterozygous gain-of-function (GOF) mutations in signal transducer and activator of transcription 1 (*STAT1*) were shown to result in autosomal dominant (AD) CMC,[7,8] which was confirmed by many other studies as the main hereditary cause of isolated CMC.[3,9–14] STAT1 is the major signaling molecule downstream of interferon (IFN) receptors. Triggered by IFNs, STAT1 translocates to the nucleus and triggers the transcription of IFN-inducible genes, which play a pivotal role in the defense against pathogens.[15] GOF *STAT1* mutations, located in either coiled-coil domain (CCD) or DNA-binding domain (DBD), leads to hyperphosphorylation of STAT1 and accumulation of phosphorylated STAT1 in the nucleus, which may shift the immune response away from a STAT3-mediated induction of Th17 cell generation.[7,8] This shift could be explained by either an increased function of cytokines, such as IL-27 and IFNs that dampen the Th17 response, or less availability of STAT1 molecules to form heterodimers with other STAT molecules, needed to induce