Rare fungal infections sometimes are recalcitrant and life-threatening, which bring a big challenge to the clinical management. Recent studies of chronic mucocutaneous candidiasis, deep dermatophytosis and some dematiaceous fungal infections have led to many breakthroughs in our understanding of host defense against fungal infections. This review summarizes important findings, including the author’s recent work, of crucial mechanisms that predispose some rare cutaneous fungal infections, including Dectin-1 deficiency, CARD9 deficiency, and STAT1 gain-of-function mutations.

**Key words**: CMC, Dectin-1, CARD9, STAT1, Th17 cells

### Introduction

Fungi are associated with a wide spectrum of diseases in humans, with increasing morbidity and mortality. Rare fungal infections, especially some recalcitrant or life-threatening infections that occur in otherwise healthy hosts, pose serious challenges to our clinical work. Therefore, it is of great importance to elucidate the genetic and immunological mechanisms underlying the susceptibility to these rare fungal infections.

Studies from the past decade have led to many breakthroughs in our understanding of host defense against fungal infections. The innate immune system is the first line of defense against pathogens and broadly protects against invading microorganisms. Pattern-recognition receptors (PRRs) exist on innate cells to recognize conserved pathogen-associated molecular patterns (PAMPs) from fungi. Among those PRRs, Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) are the major PRRs involved in antifungal immunity, which shape different downstream signaling and adaptive immune responses, especially T helper responses. This review summarizes important findings, including our recent work, of crucial mechanisms that predispose to some rare fungal infections, including Dectin-1 deficiency, CARD9 deficiency, and STAT1 gain-of-function mutations.

### Dectin-1 deficiency

Dectin-1 is one of the CLRs families, which express on myeloid cells and recognize fungal β-glucan, triggering phagocytosis and production of inflammatory cytokines. Dectin-1 deficiency is a mild immunodeficiency that was described in a Dutch family with 3 affected sisters presenting with recurrent vulvo-vaginal candidiasis, chronic onychomycosis, or both. A homozygous nonsense mutation (Y238X) in Dectin-1 resulted in the loss of a cysteine bond, which was predicted to disrupt
correct protein folding. As a consequence, cell-surface expression of the mutated receptor and the capability to bind \( \beta \)-glucan or \textit{Candida albicans} was lost. Both monocytes and macrophages from patients showed poor \textit{in vitro} production of IL-6, IL-17, and TNF-\( \alpha \) on stimulation with \( \beta \)-glucan, \textit{C. albicans} yeast, or hyphae elements. Later, Y238X was shown as a polymorphism with a heterozygosity frequency of up to 40\% in some populations. This early stop codon SNP has further been shown to be associated with increased \textit{Candida} colonization in a cohort of patients with HSCT\textsuperscript{3}, but not with systemic candidiasis, in a case-control study of patients with candidemia\textsuperscript{4}.

**CARD9 deficiency**

Caspase recruitment domain-containing protein 9 (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). 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-\( \kappa \)B) activation and innate antifungal immunity, thereby triggering the differentiation of naive T cells into T-helper (Th) 17 cells.

Chronic mucocutaneous candidasis (CMC) is a primary immunodeficiency that generally manifests itself as recurrent or persistent oral thrush, and onychomycosis. In 2009, a homozygous loss-of-function nonsense mutation in \textit{CARD9} was reported in 4 patients from a large consanguineous family with CMC\textsuperscript{5}. The Q295X mutation resulted in a premature stop codon in the coiled-coil domain of CARD9 and in the lack of CARD9 expression. Patients showed reduced TNF-\( \alpha \) production and low numbers of IL-17 producing T cells. Recently, AR CARD9 deficiencies were also discovered in patients with \textit{Candida} meningoencephalitis\textsuperscript{6}. Apart from the reduced numbers of Th17 lymphocytes, CARD9-deficient neutrophils showed a selective \textit{C. albicans} killing defect\textsuperscript{6}.

In 2014, we reported 4 Chinese patients with subcutaneous phaeohyphomycosis caused by \textit{Phialophora verrucosa}, a black fungus, with CARD9 mutations\textsuperscript{7}. We showed patients with marked decreased Th17 cells and impaired cytokine responses against \textit{P. verrucosa}. Our study linked, for the first time, CARD9 deficiencies with susceptibility to opportunistic filamentous fungi. Later on, idiopathic deep dermatophytosis and invasive exophiala infections have also been reported in AR CARD9-deficient patients, underscoring the importance of CARD9-dependent pattern recognition signaling in both mucocutaneous and invasive antifungal host defense.

**STAT1 mutations**

Signal transducer and activator of transcription 1 (STAT1), one of the 7 transcription factors of the STAT family, is the major signaling molecule downstream of the type I and type II interferon (IFN) receptors. When IFN-\( \gamma \) binds to its receptor, it causes the dimerization of the two receptor subunits and phosphorylation of Janus kinase (JAK) 1 and JAK2. The activated JAKs phosphorylate IFN-\( \gamma \)R1, followed by recruitment and activation of STAT1. By forming a homodimer, STAT1 translocates to the nucleus and triggers the transcription of IFN-\( \gamma \)-inducible genes, which plays a pivotal role in the defense against intracellular pathogens.

Heterozygous missense mutations in \textit{STAT1} were first reported in 2011 in 14 patients with autosomal dominant CMC from 5 families\textsuperscript{8}, and 12 different heterozygous \textit{STAT1} coiled-coil domain (CCD) missense mutations in 47 patients from 20 families\textsuperscript{9}. All the mutations were shown to be gain-of-function, leading to accumulation of phosphorylated STAT1 in the nucleus. Persistently activated STAT1 may shift the immune response from STAT3-mediated Th17 cells generation, which is crucial for the antifungal defense of skin and mucosa, towards STAT1-dependent Th17 inhibiting responses. Due to the high frequency of mutations, all patients suspected of CMC are suggested to first sequence for \textit{STAT1} mutations nowadays. Up till now, more than 123 CMC patients with 32 different STAT1 variants have been reported in the literature. The majority of GOF-\textit{STAT1} mutations are confirmed to be in the CCD, with 22 variants in 98 patients reported, whereas 10 variants involving 25 patients in the
DNA-binding domain (DBD) were also described. We also ascertained seven patients of Han ethnic groups in China with different clinical manifestations of CMC harboring novel and recurrent STAT1 mutations recently.

In 2013, we reported a case of a 7-year-old girl with cutaneous fusariosis recalcitrant to therapy. By using exome sequencing for this patient, we identified a de novo missense mutation in the STAT1 gene. This is the first link of primary cutaneous opportunistic fungal infections due to *Fusarium solani* with the STAT1 mutation. GOF mutation of STAT1 is also associated with a spectrum of other fungal infections, such as disseminated coccidioidomycosis and histoplasmosis, *Penicillium marneffei* infections, and disseminated mucormycosis, highlighting the pivotal role of STAT1 in fungal infections.

**Conclusion**

Rare fungal infections, especially those with early onset and recalcitrant feature, are rare but important, which have hugely promoted our understanding of immunological pathways involved in human antifungal immunity. Of course, there are still a large number of questions yet to be deciphered. We believe that collaborations from the field of dermatology, microbiology, genetics, immunology and systems biology will provide new insight into it, to develop the novel and personalized immunotherapeutic strategies in the near future.

**References**