Fungal Infections: Blame the TH-17 Cells

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Hippocrates, more than 2000 years ago, already described apthus ulcer with oral thrush in debilitated patients. In the mid-19th century it was found to be caused by fungal infection. In 1923 Christine Marie Berkhout coined the term *Candida albicans* for the most common fungus type to cause infection in humans.

While it is almost universal for an infant to suffer from 'oral thrush', a self-limited disease caused by Candida, only infants with immune deficiency will suffer from chronic recurrent oral thrush. Furthermore, adults who are immune compromised may suffer from systemic candidiasis, which can be a life-threatening event [1]. To complete the clinical picture of Candida infection, there are rare cases of individuals with chronic mucocutaneous candidiasis, which can be an isolated phenomenon or may be associated with other abnormal findings [2].

Until recently it was thought that TH1 cells were the main players in the defense against fungal infection [3]; however, current findings twist the interest towards TH17, a newly described T cell subset, and the crucial cell involved in the immunity toward fungal infection [4].

In this issue of *IMAJ* Hamoud et al. [5] describe a healthy woman with recurrent fungal infections. Although no immunological defect was found, this editorial will try to show that most probably an undefined immunological defect does exist. We will present the current knowledge regarding the immune pathway leading to killing Candida, and discuss the pathogenesis of the various rare conditions associated with CMC.

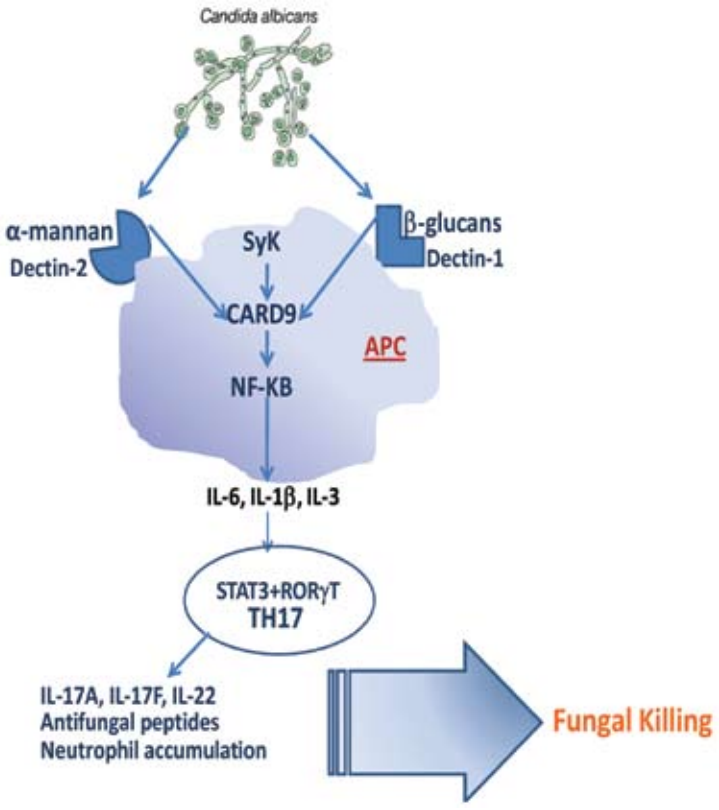
IMMUNE DEFENSE AGAINST FUNGAL INFECTIONS [Figure 1]

Traditionally, CD4 Th1 cells were thought to be involved in the immune response against Candida, mainly through its major cytokine, interferon-gamma. Later, it was found in the INFγ knockout mouse that there was no increased susceptibility to Candida infections and therefore another cell type must be involved [6].

The first step in the recognition of fungal pathogens is by cell-surface receptors that are generally called pattern recognition receptors. Toll-like receptors are the best characterized pattern recognition receptors, but several other families, such as the C-type lectins, have also been described. Indeed, 2 C-type lectins, dectin-1 and 2, have been demonstrated to be pivoted in the immune response towards Candida [7]. Both recognize different specific fungal cell wall components.

CMC = chronic mucocutaneous candidiasis
INFγ = interferon-gamma

The various components involved in the immunity against fungus



Dectin-1 recognizes β-glucan while dectin-2 will bind to α-mannan and seems to be the major pattern recognition receptor in the immune response towards fungus [8]. Binding of fungal components to the dectins will trigger the phosphorylation of the SyK tyrosine kinase, which will then activate downstream an adaptor protein known as CARD9, causing the activation of the transcription factor NF-κB. The dectin-SyK-CARD9-NF-κB signaling pathway triggers the production of cytokines, such as interleukin-1β, IL-6 and IL-23, which are essential for the generation of TH17 cells [9].

Naive CD4+Th precursor cells will develop into TH17 in the presence of these cytokines. They act in a signal transducer and activator of transcription 3 (STAT 3)-dependent manner to induce the expression of the retinoic acid-related orphan receptor (ROR)γt to induce Th17 cells. Differentiated Th17 cells secrete IL-17A, IL-17F and IL-22 cytokines, which are known to promote antifungal immunity by inducing the release of a wide range of pro-inflammatory danger signals, the expansion of antimicrobial factors, chemokine production at sites of infections, and recruitment of neutrophils [10].

Recently, it was shown that T regulatory cells, which normally suppress immune response, can promote TH17 cells to increase production of IL-17A, IL-17F and IL-22 and thus enhance host resistance to Candida infections [11].

GENETIC DEFECTS LEADING TO CMC

Until recently, the genetic etiologies of various disorders associated with CMC were unknown, although a clear autosomal recessive or dominant inheritance was observed. The hyper-immunoglobulin E syndrome has both immunological and connective tissue findings. Severe eczema, CMC, cold abscess and hyper-IgE levels are the prominent immunological parameters [12]. Several years ago, the genetic defect in most cases was found to be due to a dominant mutation in STAT3. As STAT3 is essential for the induction of TH17, it was indeed found that patients with the dominant form of HIES do not have any TH17 cells and thus do not produce any IL-17A, IL-17F or IL-22, leading to the increased susceptibility to mucocutaneous candidiasis [13].

The autoimmune polyendocrinopathy and celebral dystrophy is a rare autosomal recessive syndrome due to mutation in the autoimmune regulator gene (*AIRE*) which is essential for presenting autoantigens to T cells in the thymus, leading to clonal deletion of these T cells. As a consequence, patients with APECED suffer from multiorgan autoimmunity, mainly hyperparathyroidism and adrenal failure.

The association with CMC in this syndrome was an enigma until recently, when it was found that aside from autoantibodies against the various organs, these patients also develop neutralizing autoantibodies against IL-17A, IL-17F and IL-22 [14], which are needed for fungal killing.

Although in most cases of isolated CMC the genetic defect is unknown, several defects were recently discovered. A family with homozygous point mutation in CARD9 with loss of function has been described [15]. The CARD9-deficient patients also displayed a significantly smaller proportion of IL-17-expressing T cells and severe defect in the generation of a TH-17 response [15]. Another family with dectin-1 deficiency was also reported [16]. Still, since this family suffered from only a mild form of CMC, the role of dectin-1 deficiency in humans remains controversial.

Puel et al. [17] recently described two new genetic defects in isolated CMC. One family had a homozygous nonsense mutation in the IL-17 receptor A (IL-17RA). This mutation abrogated IL-17RA receptor expression in mononuclear cells and thus these cells become unresponsive to IL-17A or F. The second family had a missense mutation in IL-17F with autosomal dominant inheritance. The mutation was located in the cavity of the cytokine, a region implicated in receptor binding [17].

Very recently the genetic cause of most cases of the autosomal dominant form of CMC was identified. These patients were found to have mutations in the CC domain of STAT1 [18]. Although mutations in STAT1 were noted in the past to cause increased susceptibility to Mycobacteria due to a defect in the IFNγ pathway, these new CC domain mutations are gain of function mutations with increased IFNγ production and thus impaired IL-17 immunity [19].

It seems logical to assume that additional genetic etiologies related to the TH17 lineage will be found in other subjects suffering from CMC and may pave the way for developing new therapeutic strategies to improve TH17 responses.

IL = interleukin

HIES = hyper-immunoglobulin E syndrome
APECD = autoimmune polyendocrinopathy and celebral dystrophy

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