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RECEPTORS AND PATHWAYS IN INNATE ANTIFUNGAL IMMUNITY:

THE IMPLICATION FOR TOLERANCE AND IMMUNITY TO FUNGI

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1. INTRODUCTION

In the last years, the clinical relevance of fungal diseases has gained importance because of an increasing population of immunocompromised hosts, such as patients who have undergone transplants, patients with various types of leukemia, and people infected with HIV. Although some virulence factors are of obvious importance, pathogenicity cannot be considered an inherent characteristic of fungi.[1] Fungi seem to have a complex relationship with the vertebrate immune system, mainly due to some prominent features: among these, the ability of dimorphic fungi to exist in different forms and to reversibly switch from one to the other in infection. Although association between morphogenesis and virulence has long been presumed for fungi that are human pathogens[2], no molecular data unambiguously establish a role for fungal morphogenesis as a virulence factor. What fungal morphogenesis implicates through antigenic variability, phenotypic switching, and dimorphic transition is the existence of a multitude of recognition and effector mechanisms to oppose fungal infectivity at the different body sites.

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Most fungi need a stable host–parasite interaction characterized by an immune response strong enough to allow host survival without pathogen elimination, thereby establishing commensalisms. Therefore, the balance of proinflammatory and antiinflammatory signaling is a prerequisite for successful host–fungus interaction. In light of these considerations, although developments in fungal genomics may provide new insights in mechanisms of pathogenicity[3], the responsibility for virulence, regardless the mode of its generation and maintenance, is shared by the host and the fungus at the pathogen–host interface. Studies with *Candida albicans* have provided a paradigm that incorporates contributions from both the fungus and the host to explain the theme of the origin and maintenance of virulence for commensals. Through a high degree of flexibility, the model accommodates the concept of virulence as an important component of fungus fitness in vivo within the plasticity of the host immune system[4].

2. WHAT AND WHICH ARE OPPORTUNISTIC FUNGAL PATHOGENS?

The human commensal *C. albicans* is the leading fungal cause of important diseases in humans[5]. *Candida* is a polymorphic fungus; it can exist in different forms that have distinct shapes: yeast cells, pseudohyphal cells, and true hyphal cells, all of which can be found in infected tissues. The ability to switch from yeast to filamentous form is required for virulence, but much of the evidence linking transition and virulence remains equivocal. The clinical spectrum of *C. albicans* infections ranges from mucocutaneous to systemic life-threatening infections. The predisposing factors to severe candidal infections can be congenital or acquired and concern defects of cell-mediated immunity, including defects in neutrophils and dysregulated Th cell reactivity.

Most fungal infections are of exogenous origin. A striking example is *Aspergillus fumigatus*, a saprophitic and ubiquitous fungus, for the ease of dispersion of its conidia. The diseases caused by *Aspergillus* range from benign colonization and allergy to deadly diseases such as invasive pulmonary aspergillosis.[6] The small conidia can remain in suspension in the environment for a long period of time, reaching human pulmonary alveoli and constantly exposing individuals inhaling them. In immunocompromised hosts, such as neutropenic patients or transplanted patients undergoing graft-versus-host disease, the inhalation can provoke serious diseases, consisting of host tissue invasion by conidia germinated to septate hyphae, an invasive form associated with fatal infections.

3. THE IMMUNE RESPONSE TO FUNGI : FROM MICROBE SENSING TO HOST DEFENCING

Protective immunity against fungal pathogens is achieved by integration of two distinct arms of the immune system — the innate and adaptive (or antigen-