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Alarmin(g) the innate immune system to invasive fungal infections

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Fungi encounter numerous stresses in a mammalian host, including the immune system, which they must adapt to in order to grow and cause disease. The host immune system tunes its response to the threat level posed by the invading pathogen. We discuss recent findings on how interleukin (IL)-1 signaling is central to tuning the immune response to the virulence potential of invasive fungi, as well as other pathogens. Moreover, we discuss fungal factors that may drive tissue invasion and destruction that regulate IL-1 cytokine release. Moving forward understanding the mechanisms of fungal adaption to the host, together with understanding how the host innate immune system recognizes invading fungal pathogens will increase our therapeutic options for treatment of invasive fungal infections.

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Introduction

Fungi are ubiquitous in nature and, for the most part, are harmless to the majority of individuals. However, it is estimated that 2 million cases of invasive mycoses are reported worldwide each year [1]. These invasive mycoses occur primarily in immunocompromised patients. Thus, in the absence of an adequate innate host defense, these opportunistic pathogens can infect the host and lead to disease. Furthermore, invasive fungal infections continue to be a rapidly emerging and serious threat because of the growing immunocompromised population and the emergence of drug resistance [1].

Candida spp. and *Aspergillus* spp. are known to cause approximately 30% of all invasive fungal infections [1]. However, the environmental niche filled by *Candida* spp. and *Aspergillus* spp. substantially differs, which could drive evolution of distinct adaptation traits necessary for virulence. *Candida* spp. are found as a normal commensal component of the human skin, gastrointestinal tract and other mucosal surfaces [2], whereas *Aspergillus* spp. are saprophytic molds found in the environment on decaying organic material [3]. Hundreds of species exist within the *Candida* and *Aspergillus* genera, but only a handful have been shown to cause invasive mycoses in humans. Even though mortality rates for invasive fungal infections have significantly decreased in the past decade [4], mortality rates from invasive candidiasis and invasive aspergillosis are unacceptably high, ranging anywhere from 20 to 50% due to limited diagnostic tools and lack of effective treatment options [4–9]. Thus, novel therapeutic targets for anti-fungal drugs are desperately needed. Fungal factors driving adaption and growth in the mammalian host offer great potential as novel anti-fungal targets. In addition, tuning the host inflammatory response to confer optimal host resistance is another exciting avenue for limiting invasive fungal infections.

Innate immunity is essential for resistance against *A. fumigatus* and *C. albicans*. Patients with primary immunodeficiencies in the NADPH oxidase complex, STAT3 signaling pathway, CARD9 signaling pathway, IL-17 immunity, leukocyte adhesion deficiencies, and those with severe congenital neutropenia have been shown to be predisposed to developing invasive fungal infections (reviewed in [10,11]). Moreover, polymorphisms in numerous innate immune sensing and signaling pathways alter the susceptibility of transplant patients to developing invasive fungal disease (reviewed in [11–13]). In this review, we discuss the importance of interleukin-1 (IL-1) in tuning the inflammatory response in the context of invasive fungal disease. Moreover, we highlight the potential importance of this model broadly across the spectrum of infectious diseases. We highlight recent data which demonstrate that the mammalian innate immune system responds in a regulated manner that is tuned to the level of growth, virulence, and pathology induced by the fungal pathogen.

Alarmins/damage-associated molecular patterns (DAMPs) versus microbial-associated molecular patterns (MAMPs)

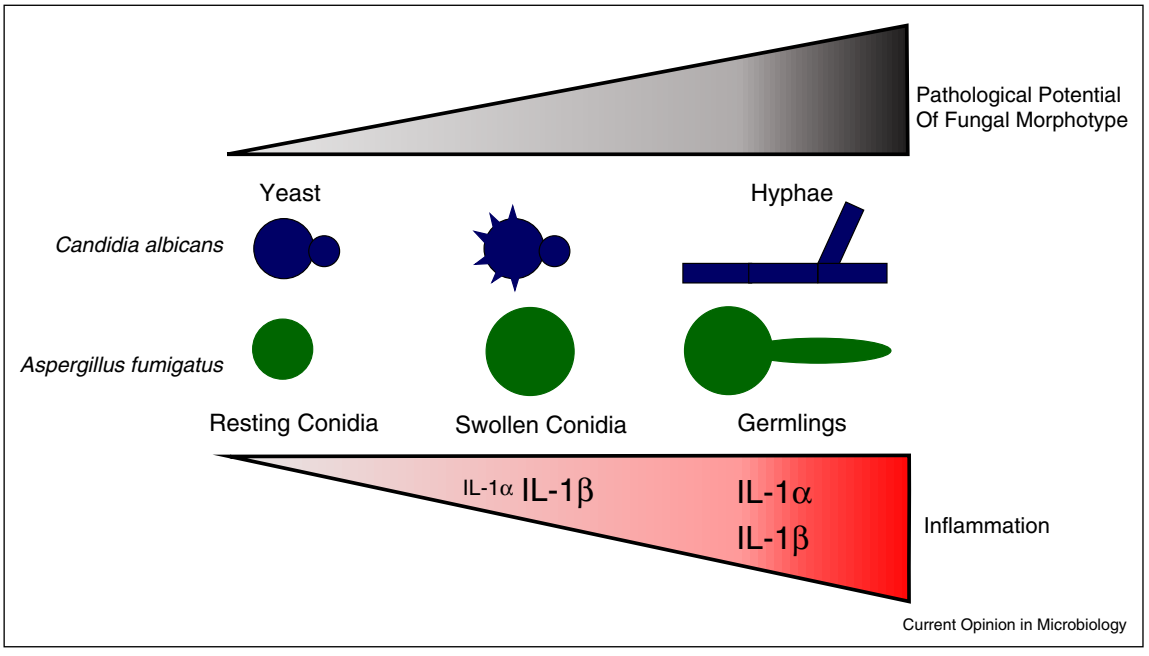
The innate immune system provides an essential early response to microbial infection. Initial sensing of microbes has been well established to be mediated by

a series of germline-encoded host pattern-recognition receptor (PRR) families, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), Nod-like receptors (NLRs), and RIG-I-like receptors (RLRs), which can recognize conserved microbial structures termed microbial-associated molecular patterns (MAMPs). Examples of MAMPs of particular relevance to fungal pathogens include β-1,3-glucan, chitin, mannans, mannoproteins, and unmethylated DNA. However, all fungi whether pathogenic to the host or not will express these MAMPs. To address the conceptual problem of pathogen *versus* commensal organism, Vance and colleagues have proposed that it is not just the MAMP that is critical for immune cell activation, but also its location within the host and/or cell, which they termed the 'patterns of pathogenesis' [14••]. These early pathogenic signatures will instigate the inflammatory response following fungal exposure. During the course of invasive fungal infections, fungal growth and invasion into the body, together with the host immune response will cause significant tissue damage, extracellular matrix destruction, and cell death at the site of infection. Tissue destruction and cell death during infection is highly inflammatory due to the release of damage-associated molecular patterns (DAMPs) or alarmins from the dying host cells [15,16]. These alarmins include both non-protein materials, such as ATP and uric acid, as well as proteins, which include IL-1α, IL-33, S100 proteins, and HMGB1. Thus, during invasive fungal infections initial inflammation will be regulated by PRRs, but if that response is insufficient to prevent invasive growth, alarmin release due to tissue destruction and host cell death will amplify the magnitude of the inflammatory response to attempt to regain control (Figure 1).

Basics of the IL-1 cytokines in inflammation

The IL-1 gene cluster codes for the cytokines IL-1α and IL-1β, as well as the IL-1 receptor antagonist (IL-1ra), all three of which can bind to the IL-1 receptor, type I (IL-1RI) [17]. While IL-1α and IL-1β are pro-inflammatory cytokines, IL-1ra competitively binds the IL-1RI to dampen the immune response [17]. Although IL-1α and IL-1β belong to the same cytokine family, they rely on different proteases and cell death pathways for their secretion. IL-1β is produced as an inactive precursor termed pro-IL-1β that must first be transcriptionally upregulated [18]. For secretion, pro-IL-1β must then be cleaved by a caspase-1 or caspase-8 containing inflammasome, which is formed following NLR activation [18].

Figure 1



An escalating IL-1 inflammatory response regulates mammalian resistance to invasive, pathological fungal infection. In homeostatic conditions when the barrier to mucosal surfaces is intact, *C. albicans* and *A. fumigatus* can be found in a resting state on mucosal surfaces and in the airways, respectively. Once this primary immune barrier is breached, fungi can access nutrients necessary for growth. In the case of *C. albicans*, rearrangement of the cell wall occurs during phagocytosis, while in the case of *Aspergillus* spp. the cell wall architecture is changed upon conidial swelling. In either case, fungal MAMPs are revealed to the immune system resulting in the activation of an inflammasome-dependent immune responses to clear the fungal threat. If the fungi continue to grow forming invasive hyphae and express hyphal-specific effectors, which may include GAG, secondary metabolites, and proteases, robust tissue pathology can result. This increased pathology drives elevated levels of pro-inflammatory cytokines and alarmin release, such as IL-1α, which intensify the innate immune response in hope of clearing the infection. Font size for each cytokine is indicative of their relative abundance.