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Host-microbe interactions: fungi

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The past three decades have seen a dramatic jump in the incidence of invasive fungal infections, mostly as a result of an increased population of susceptible immunocompromised patients. Many important fungal diseases are associated with specific immunological conditions: cryptococcal meningitis and AIDS, disseminated candidiasis and neutropenia, aspergillosis and bone marrow transplantation. The focus on immune dysfunction in these cases should not, however, give the impression that a healthy immune system easily dispatches fungal pathogens. *Coccidioides* and *Histoplasma* cause disseminated infections in otherwise healthy people and fungi cause a wide variety of common skin and mucosal diseases, without any underlying immune compromise. Currently, in British Columbia, Washington and Oregon, an opportunist is crossing the line to become a primary pathogen, in an outbreak of cryptococcosis caused by *Cryptococcus gattii* [1,2]. For disseminated candidiasis, a medical intervention as simple as an intravenous catheter is a significant risk factor. Thus, even if most of us avoid serious fungal infections, the human immune system appears to walk a fine line in the control of these pathogens.

It has been long appreciated that fungal pathogens have both active and passive mechanisms to thwart the immune response. *Candida albicans* germ tube formation within macrophages was described as early as 1969 [3]. The cryptococcal capsule was recognized as a barrier to phagocytosis in the 1980s [4], and other immune evasion properties had been ascribed to the capsule even earlier. Goldman and colleagues documented the ability of *Histoplasma capsulatum* to block phagolysosomal acidification in 1993 [5]. More recent discoveries are no less remarkable: *Cryptococcus* escapes macrophages via ballistic expulsion [6], though the mechanism is not yet understood. *C. albicans* starts begins its anti-oxidant defense outside the cell through novel secreted forms of superoxide dismutases [7]. The *H. capsulatum* yeast-specific protein CBP1 has been shown to have a similar structure to mammalian saposins, and is implicated in binding and alteration of the phagosomal membrane [8]. Several reviews in this section expand upon recent additions to these anti-immunity phenomena, including fungal-induced alterations in phagosomal maturation and inhibition of reactive oxygen species production (Seider, et al.), routes to reduce complement deposition on the cell surface (Seider, et al., Brakhage, et al), and the masking of immunogenic epitopes on the cell surface (Seider, et al., Lenardon, et al.).

Just as the immune system has multiple responses to fungi, it has become clear that individual immune cells also have multiple mechanisms for recognition of fungi. In this section, Kuchler and colleagues outline the known receptors and pathways in phagocytes, especially in the context of *Candida* species (Bourgeois, et al.). They describe no fewer than nine receptors that

recognize fungal pathogen-associated molecular patterns, mostly polysaccharides of the cell wall. Figure 1 of their review conveys the remarkable progress made in understanding the complexity of these molecular interactions and, at the same time, the limited knowledge we currently have concerning the integration of these various signals to produce an effective antifungal response.

Brakhage, et al., focus on the interaction of filamentous fungi with different components of innate immunity, including phagocytes and the complement system. Nevertheless, as they point out, the molecular interactions between cell surface moieties on the fungus and host receptors share many similarities – including the complexity – with phagocyte-yeast interactions. Another level of complexity appears in this review – neutrophils are absolutely critical in the early stage of a challenge with *A. fumigatus*, and dispensable thereafter. Such a temporal progression makes perfect sense, as the fungal pathogens undergo differentiation and dissemination during the course of infection, but we are only beginning to understand the immune response at this level.

The phagocyte receptors relevant to antifungal immunity are almost exclusively targeted to pathogen-associated molecular patterns (PAMPs) on the cell surface. For the most part, these are oligosaccharides, and most attention has been paid to mannans and glucans. Lenardon, et al., focus on chitin, an N-acetylglucosamine polymer found in all fungi and many invertebrates, but not in mammals. Given its absence from mammals and essential nature, chitin synthesis is an attractive chemotherapeutic target but, to date, has not been clinically efficacious despite some effort, perhaps complicated by the many subtypes of chitin synthases, the distribution and function of which are not completely understood. The immunogenicity of chitin is determined by several factors, including polymer size, and is probably context dependent. Many fungi, however, mask chitin under a layer of mannan and/or glucan, thus shielding it from immune detection.

This last point – evasion of immune detection by masking PAMPs – is part of an increasing realization that fungal pathogens employ sophisticated mechanisms to evade or suppress immune responses. Seider, et al., discuss several of these, including masking of glucans in *C. albicans* beneath an outer mannoprotein layer. *Candida*, *Aspergillus* and *Cryptococcus* all possess mechanisms to dampen the complement response, including the binding of complement regulators like plasminogen and Factor H, or by binding and blocking complement receptors (see Seider, et al., and Brakhage, et al.). Hube and coauthors (Seider, et al.) also discuss other approaches for immune evasion or suppression, including alterations in phagocyte function, phagosome maturation, and inhibition of reactive oxygen species production.

Two reviews in this section discuss regulatory mechanisms relevant to the host-pathogen interaction. Calderone and coauthors discuss the roles of the fungal histidine kinases, a signaling module analogous to the hybrid histidine kinase family of bacterial two-component systems. The fungal-specific proteins are intimately involved in stress responses in all of the species in which they have been studied, particularly oxidative and cell wall stresses via the MAP kinase HOG1, and are thus key mediators of the fungal response to the host killing mechanisms. As these authors discuss, these signaling proteins have been associated with virulence in several species, including *C. albicans*, *C. neoformans*, and *Blastomyces dermatitidis*, and remain to be studied in many other species.

Filamentous fungi, in particular, secrete a large number of so-called secondary metabolites, small molecules that are assumed, and in some cases proven, to affect interactions with both environmental competitors and host cells as toxins and antimicrobials. The genomic organization of the synthetic enzymes (most secondary metabolites are produced in a multistep

process involving several gene products) is quite unusual for fungi – genes for a single metabolite are clustered on the chromosome, and frequently found in subtelomeric regions and are subject to both genetic and epigenetic control. Palmer and Keller review the genome structure and regulation of these clusters, highlighting *LaeA*, a global regulator of secondary metabolism in *A. fumigatus*. Mutants lacking *LaeA* are avirulent in an inhalational model of aspergillosis, confirming the importance of these secondary metabolites in host-pathogen interactions.

The final two reviews in this section represent new revelations in fungal-host interactions. In the first, Botts and Hull describe the characterization and importance of cryptococcal spores. As well as having the standard properties of fungal spores (easily dispersible and stress resistant), these spores have long been assumed to be the infectious particle, via inhalation. Only in the last few years, however, has a protocol been developed to isolate spores in sufficient quantities to test their role in transmission and during an infection. Validating the long-held assumption, the spores are infectious and have interactions with phagocytes that are vastly different than those of yeast cells. While yeast are mostly invisible to alveolar macrophages, spores are rapidly phagocytosed. Spores germinate within the macrophage in a race against time: if the spore germinates before the macrophage is activated, it survives and can disseminate within the phagocytes; if the macrophage is activated first, it efficiently destroys the cryptococcal cell. These are certain to be just the first of many important revelations regarding these spores.

Finally, Delbac and colleagues describe the interaction of the host with the microsporidia. These obligate parasites were definitively classified as fungi only a few short years ago, and they exhibit a new paradigm of host-fungal interactions with their compact genomes and intimate association with animal cells. Outside of animal cells, they survive only in the spore form; infection is mediated by a remarkable structure, the polar tube, which injects the “sporoplasm” into the host cell. Microsporidial infections in humans are generally asymptomatic, kept in check by avid cell-mediated immune responses and so infections are problematic particularly in AIDS patients. A vast diversity of microsporidia can infect animals of all sorts, and new models are being developed to continue the progress on these “new” fungi.

The last 15 years has seen a dramatic jump in the genetic tools, genomic resources, and research communities for the most important fungal pathogens. This has powered a flood of remarkable work on host-pathogen interactions. Yet, the answers to questions often lead to several unanswered ones, as is the case in much good science, confirming that we have a long way to go to fully understand the biology of fungi in the context of the mammalian host.

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Biography

Mike Lorenz is in the Department of Microbiology and Molecular Genetics at the University of Texas Health Science Center in Houston, a group with broad interests in microbial physiology and host-pathogen interactions. He has had a long-standing interest in the interaction of *Candida* with host immune cells, and his research focuses on the changes in gene regulation, metabolism, and physiology of the fungal cell upon interaction with phagocytes.