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Current Opinion in Microbiology

# Fungal infections: the next challenge

## Editorial overview

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**Current Opinion in Microbiology** 2012, **15**:403–405

For a complete overview see the Issue

Available online 31st July 2012

1369-5274 

http://dx.doi.org/10.1016/j.mib.2012.07.002

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Gordon Brown completed a PhD in microbiology at the University of Cape Town, South Africa. He was a Wellcome Trust travelling postdoctoral fellow at the University of Oxford, UK, then a Wellcome Trust Senior Fellow at the University of Cape Town, South Africa, and is now a Professor of Immunology at the University of Aberdeen. His primary research interests are macrophage receptors and their role in immunity and homeostasis.

Fungal infections caused by various fungal species have become a leading cause of morbidity and mortality in the last decades. Although not recognized as such for a long period of time, mainly because of the traditional view that bacteria, viruses or parasites are the main human pathogens, there is increasing awareness that fungal infections cause as heavy a burden on human health as these other organisms [1]. In the Western societies, the high burden of fungal infections is especially true for the severely ill patients, both immunocompetent and immunocompromised, who have an increased risk of nosocomial fungal infection. In contrast, in developing countries a large array of fungal infections affect both immunocompromised (e.g. HIV-infected) and otherwise healthy individuals [1]. Despite the discovery of novel and more potent antifungal drugs against the major fungal pathogens (*Candida*, *Aspergillus*, and *Cryptococcus* spp.), the mortality due to fungi remains high, in the range from 30 to 50%, and it is believed that adjunctive immunotherapy is the only approach that could improve this grim outcome [2].

In order to be able to propose innovative new approaches for adjunctive immunotherapy of fungal infections, a very solid knowledge on both the pathogens and the host defense mechanisms against these organisms is needed. The last years have witnessed a spectacular increase in our understanding of fungal pathogens and infections, and in this issue of *Current Opinion in Microbiology* an overview of some of the most important of these advances are presented.

In the first review of this series, Gow and Hube present an overview of the current knowledge of the importance of the cell wall of *Candida albicans* during commensalism and infection, a crucial step in understanding the host defense against this most important human fungal pathogen. Firstly, the authors review the cellular and molecular mechanisms that *Candida* employs for the various stages of invasion: adhesion, invasion, and endothelial damage, and the molecular changes during yeast-hyphal transformation underpinning these processes. Secondly, the authors describe the important knowledge obtained in the last decades on understanding recognition of *Candida* by the innate immune system, the first and main line of immunological defense against the pathogens. The crucial role played by polysaccharide structures of the cell wall (e.g. mannans, β-glucans or chitin) that are recognized by pattern-recognition receptors is explained. Furthermore, they discuss the interplay between *C. albicans* and epithelial cells, neutrophils and macrophages/Th17 cells at the level of the mucosa during colonization and infection. The authors conclude that the transition of *C. albicans* from commensalism to invasive growth is a shift in the dynamic equilibrium between host and pathogen associated factors, for which the fungus has evolved mechanisms to counter the effects of the sentinel activity of

mucosal immunity mechanisms. Understanding this process could provide new targets for therapy.

An important subsequent step is the assessment of the importance of these mechanisms *in vivo*. In this respect, animal models of fungal infections play a crucial role, on the one hand by mimicking the infection in the patients, and on the other hand by allowing the study of genetic or immunologic depletion of certain components of the antifungal defense mechanisms. Steele and Wormley present an overview of the role played by animal models of fungal infections in understanding the crucial steps necessary for an effective fungal elimination: the recognition by pattern recognition receptors such as Toll-like receptors and C-type lectin receptors, the role of polarization of cellular immune responses towards Th1 or Th17, and the role of antibody-mediated mechanisms of anti-fungal host defense. They conclude that animal models of fungal pathogenesis have provided great insight into what occurs following the interaction of fungi with various innate and adaptive immune cells.

Not only experimental animal models can help us in understanding host defence against fungi, but also the 'experiments of nature' encountered in patients with primary immunodeficiencies and an increased susceptibility to fungal infections. In the review by Lilic in this number of *Current Opinion in Microbiology*, we are presented with a systematic description of the important defects in immunological mechanisms leading to recurrent and/or severe fungal infections. Recent work has demonstrated the pivotal role of Th17 responses for the mucosal antifungal defects, and genetic defects in genes such as *STAT1*, *STAT3*, *IL-17F*, *IL-17R*, *dectin-1*, *CARD9* or *AIRE* have all been associated with mucosal fungal infections in the various variants of chronic mucocutaneous candidiasis syndromes described in the literature. In addition, classical immunodeficiencies such as severe combined immunodeficiency, CD4 lymphopenia or chronic granulomatous disease are associated with systemic fungal infections. The discovery of the mechanisms defective in these patients has proven crucial for understanding the underlying pathways mediating host defence in common infections with fungi, and for designing effective vaccination or immunotherapy.

The step towards immunotherapy of fungal infections is proposed in the next two reviews in the series. In the first of these reviews, Cassone and Casadevall discuss the progress and the future perspectives on the development of vaccines against the major fungal pathogens. The authors contemplate the chain of events that have precipitated the progress in the research for fungal vaccines in the last years, including the medical plight of millions of patients suffering from conditions such as recurrent vulvovaginal candidiasis (RVVC, currently a major target for vaccine development) or systemic fungal infections in the immunocompromised host, to the dedication of several pioneering groups of investigators in the field. The authors define the groups of patients most at need for vaccination, and discuss the critical role played by the combination of a proper antigenic component and a carefully tailored adjuvant for the efficiency of a vaccine. Indeed, the recent knowledge gained in the role played by humoral or cellular (Th1/Th17) immunity in the protection against fungi gives the hope for vaccine strategies adjusted to each patient group, and each of these immune mechanisms are employed by the two vaccines currently in phase I trials for RVVC.

Next to vaccines, immunotherapeutic approaches in the already-ill patient should also be considered. Armstrong-James and Harrison discuss in their review the novel immunotherapeutic approaches employed in patients with fungal diseases, therapies that aim to boost or aid the host defense of the host. The authors discuss the promising prospects of using recombinant cytokines such as interferon-γ for the treatment of systemic fungal infections, and the potential role of antibody-based immunotherapy. These already-tested approaches are complemented in the vision of the authors by the possibilities of employing in the future additional forms of immunotherapy such as cell-based therapies using adoptive transfer of T-cells, DCs or neutrophils, while other humoral approaches such as recombinant pentraxins are also further in the pipeline. Gene therapy for severe conditions such as chronic granulomatous disease is also contemplated, and the authors conclude that all these approaches hold great promise for the future of treatment of fungal diseases.

While the progress towards understanding the host defense mechanisms against fungi is undeniable, and several of the target therapies have been or are currently tested, one should not be complacent and cease exploring new paths towards understanding host defense, leading to novel drug discovery. In the last review of this series, Tierney and colleagues present one of the most innovative approaches to understand host defense against fungi that is hoped to represent the next step in understanding the interaction between the host and the pathogens. The authors present the state-of-the-art systems biology approaches that are beginning to be employed in the study of fungal–host interaction, including transcriptomics-based and functional genomics approaches (both at the level of the host and fungus), genome dynamics of the fungal pathogen, and infection modeling. The authors are confident that systems biology holds the promise of helping us to obtain holistic views on the extent of host–fungal interaction, and to generate predictions of host–microbe behavior and disease outcome. Combining mathematical modeling and functional genomics is proposed as an approach to decipher the infectious processes and

improve the immunotherapeutic approaches to fungal infections.

In conclusion, the reviews of these series highlight on the one hand the state-of-the-art research in understanding the interaction between the pathogenic fungi and the host, and on the other hand the promising new avenues towards an effective adjuvant immunotherapy in fungal infections. As the field progresses, it is time to be optimistic that in the not very distant future novel therapeutic strategies aimed at disrupting fungal survival mechanisms and augmenting the host defenses will be designed and successfully deployed in patients with fungal infections.

## Acknowledgements

The authors thank the Wellcome Trust, Medical Research Council (UK) and the Netherlands Organization for Scientific Research for funding.

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