**Host-Microbe Interactions: Fungi**

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Fungi are ubiquitous and we are constantly exposed to these eukaryotic microbes through acquisition from the environment, particularly the inhalation of fungal spores, or as part of the microbiome on our skin, mucosal surfaces and in our gastrointestinal tracts. Most fungi do not represent a serious threat to human health, but there are a few species which can cause life-threatening invasive diseases in immunocompetent individuals. Fortunately, the incidence of these infections is "relatively" rare. Fungi also cause superficial infections of the hair, skin, nails and mucosal membranes that are normally non-life threatening and easily treatable, but affect at least a quarter of the world's population. Exposure to fungi is also thought to contribute significantly to allergies and asthma, which affects millions of people worldwide. Over the last few decades, however, there has been dramatic increase in the number of invasive infections caused by environmental and commensal fungi occurring in individuals whose immune function is compromised through modern immunosuppressive medical interventions and HIV/AIDS. In fact the numbers of deaths caused by these organisms is thought to exceed that of malaria and rival that of tuberculosis, and invasive fungal infections have some of the highest mortality rates of any infectious disease; exceeding 50% even with the best medical care. Our ability to tackle these unacceptably high rates of mortality stem from several factors, including difficulties in diagnosis and an insufficient antifungal armamentarium. Understanding the antifungal immune response is an area of considerable interest, given that defects in immunity underlie susceptibility to most invasive fungal diseases. In this issue, we focus on our current understanding of the impact of fungal interactions on the skin, mucosal surfaces, airways, gastrointestinal tract and during invasive disease. We also focus on the antifungal immune response and how immunity may be manipulated to combat fungal disease.

Although a handful of human fungal pathogens are geographically restricted, the majority are environmentally widespread (e.g. *Aspergillus, Cryptococcus* and Mucormycete species) or reside as part of the normal human commensal microbiota (*Candida* and *Malassezia* species). Consequently, understanding the factors that govern the switch between tolerance/eradication or disease is a key

challenge for fungal pathogenesis research. Hall and Noverr discuss the case of *Candida albicans*, a leading life-threatening fungal infection of humans worldwide. Unlike most fungal pathogens, *C. albicans* has evolved closely together with humans and consequently in most situations damage to the host represents an inappropriate host immune response. However, *C. albicans* also has a considerable range of weapons that it can deploy against the host, including the recently identified toxin Candidalysin covered elsewhere in this issue by Naglik and colleagues. Hall and Noverr discuss how these recent findings integrate into the "damage-response framework" first proposed by Casadevall and Pirofski [1] and propose a model of symbiosis that exists as a function of limited host damage.

How fungi deal with nutrient stress is also key to their ability to survive in the host. Baltzer and Latge discuss the importance of metal homeostasis in *Aspergillus fumigatus*, a saprophytic organism that causes a whole range of human diseases from allergy to invasive infections. Being able to both assimilate metals required for growth, while simultaneously combat metal-mediated toxicity, requires a delicate balancing act involving carefully regulated processes that are integral to the virulence of the organism. A greater understanding of these complex mechanisms are likely to provide novel therapeutic approaches in the future.

The other major fungal group found in close association with humans are the *Malassezia* species, which dominate the skin microbiota across most of the body. As Grice and Dawson describe, these species show considerable similarity to their plant-associated evolutionary cousins, including a remarkable panoply of lipid modification pathways, many of which impact on host immune signalling. Although most of us live comfortably together with our *Malassezia* residents, their ability to generate toxic by-products or to trigger inflammation occasionally leads to debilitating illness. Our investigation of this fungal group remains in its infancy, but the revolution in metagenomics studies is beginning to uncover their secrets.

Similar approaches are also unveiling the extraordinary diversity of the gut microbiome. Although studies of gut-resident bacteria have been ongoing for many years, it is only relatively recently that researchers have begun to consider the fungal components of the microbiome. As discussed by Underhill and colleagues, this long-neglected set of organisms may have a major impact on human health. In particular, there is now growing evidence that the relative balance of different fungal species within the gut may be either protect against, or contribute towards, a range of inflammatory gut

conditions. Ultimately, being able to modulate the balance of fungal species in the gut may thus offer the opportunity to profoundly alter our treatment of these disabling conditions.

For fungal pathogens that are not resident commensals, the first point of entry to the human body is often the mucosal epithelium of the lung or gastrointestinal tract. Two reviews in this issue describe recent advances in understanding this host-pathogen interface. Klein and colleagues explore how the lung responds to the presence of fungal invaders and how, on occasion, this response to can wrong, leading to allergy and asthma. Similarly, Naglik and colleagues consider the molecular basis of epithelial immunity to fungi, with a particular focus on how the body discriminates between the presence of commensal, versus invasive, *Candida* species. Both of these reviews demonstrate the fine balance that the immune system must strike between preventing severe infection and yet not "over-reacting" to common fungal antigens.

Fungal infections with Mucormycete species are relatively infrequent. However, as Voelz and Ibrahim describe, these represent some of the deadliest fungal infections we know of, with mortality rates in excess of 90%. This largely represents a paucity of treatment options available for this fungal group, but a series of discoveries in recent years may provide a glimmer of hope on the horizon. In particular, exciting advances in understanding how these organisms attach to mammalian cells, scavenge essential micronutrients and disseminate through the host, may provide for new therapeutic angles in the near future.

Although geographically restricted and consequently less numerous than opportunistic fungal disease, primary fungal infections are a major health concern in affected areas and an intriguing evolutionary enigma: what is it that allows these handful of species to cause life-threatening disease despite a robust human immune response? Rappeleye and colleagues consider these questions in the context of one major primary pathogen, *Histoplasma capsulatum*, and demonstrate that its ability to invade the host hinges on a remarkable capacity to hijack phagocytic cells of the host. To do so, Histoplasma relies on a unique and diverse armoury of virulence factors, which are only recently beginning to be deciphered.

Considerable effort has focussed on those fungi which predominantly cause invasive disease in immunocompromised individuals. One of the best studied of such pathogens is *Cryptococcus neoformans*, which is responsible for more than 250 000 deaths in individuals suffering from HIV/AIDS[i]. Some of the more recent discoveries in this area have expanded our understanding of the

early events post infection, as discussed by Ballou and Johnston in this issue, and have revealed how environmental factors both trigger and impact on, spore germination and viability once inhaled into the lung from the environment. The induction of cell division has been found to be critical for the regulated expression of key pathogenicity factors, including capsule size and structure, although the mechanisms integrating these processes remain unclear. Yet there remain important gaps in our knowledge, particularly regarding interactions with phagocytes, such as the pattern recognition receptors involved in yeast or spore uptake. In fact, even the mechanism(s) by which the fungus invades the central nervous system is still unclear.

*Pneumocystis jirovecii* is another opportunistic fungal pathogen that kills at least as many immunocompromised people as *C. neoformans*, yet is far less well studied. The inability to culture this organism *in vitro* has significantly hindered progress in this field. The worldwide epidemiology of this organism is also not well described, because of diagnostic insufficiencies, but in low and middle-income countries is thought to occur primarily in HIV+ individuals. In the western world, however, as discussed by Hoving and Kolls, the successful control of HIV has seen the prevalence of pneumocystis infections shift to the HIV-negative cases, including those suffering from haematological malignancies, on high dose corticosteroids and those with primary immune deficiencies affecting T-cell function. Macrophages are the key cell type responsible for killing the pathogen and T-cell function is also essential, but how T-cells actually mediate their protective activity is unclear.

Patients with primary immunodeficiencies have provided significant insights into the mechanisms underlying antifungal immunity, an area of medical mycology which has advanced considerably over the last two decades. One particular group of patients, covered in the review from Li and colleagues, are those with genetic defects in IL-17 immunity that predisposes individuals to chronic mucocutaneous candidiasis (CMC). In fact, defects in CD4 T-cell function, as well as mutations in IL-17, its receptor and downstream signalling components are all associated with susceptibility to CMC. Mutations in CARD9, which functions as the major adaptor downstream of C-type lectin receptors, which induce Th17 and other key responses, leads to the most severe phenotypes, increasing susceptibility to CMC and subcutaneous infections but also to invasive infections by several fungal species.

The central role of C-type type lectins in triggering key innate and adaptive antifungal immune responses is another area of intense interest. These receptors recognise the main carbohydrate constituents of the fungal cell wall, including mannan, β-glucan and chitin. In this issue, Shiokawa,

Yamasaki and Saijo present an overview of the roles and functions of each of the major C-type lectin receptors involved in antifungal immunity (Dectin-1, Dectin-2, MINCLE and MCL), as well as describing some of the new insights into their roles in regulating the composition and immunological impact of the fungal constituents of microbiome. All these receptors utilise the Syk/CARD9 pathway to induce intracellular signalling, and while we do not yet fully understand how receptor specific responses are induced, several new components of this pathway have recently been identified, many with therapeutic potential.

Understanding the antifungal immune response offers considerable potential for the development of new immunotherapies to treat patients suffering from invasive infections. In the final review of this issue, Scriven and colleagues, present an overview of the current state of the art in this field. They highlight some of the problems that are faced in reversing immune suppression, such as immune reconstitution inflammatory syndrome, as well as some of the promising adjunctive immunotherapeutic approaches that are being developed, such as administration of pro-inflammatory cytokines. Other areas of current investigation include the transfusion of leukocytes, in the setting of neutropenia for example, or adoptive transfer of pathogen-specific or chimeric antigen receptor T cells. Treatment with antifungal antibodies and the development and antifungal vaccines also show promise, and are areas of active investigation. It is notable that there is not a single antifungal vaccine in current clinical use.

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[1] Casadevall A, Pirofski L-a: The damage-response framework of microbial pathogenesis. Nat Rev Micro 2003, 1:17-24.

[i] http://www.gaffi.org/why/fungal-disease-frequency/