



Editorial: Immunological Memory to Fungal Infections and Vaccine Development

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Editorial on the Research Topic

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Throughout human history, infectious diseases have been one of the leading causes of death. However, due to advances in modern medicine, life expectancy and the total population increased considerably. Among the key drivers of this major change, vaccines have led to the elimination or significant reduction in the burden of several viral and bacterial diseases. Unfortunately, none of the clinically available vaccines target fungal diseases, which have been estimated to cause some 1.5 million deaths each year (1). Given that the more traditional vaccine technologies failed to yield effective immunization for invasive mycoses, a deeper understanding of the host response to fungi and the development of new technologies are both necessary before vaccine-mediated reductions in the burden of systemic fungal diseases are apparent. This research topic highlights some of the cutting-edge research and technological development done recently in this area.

While some invasive fungal infections are acquired, others originate by commensal outgrowth. Given that vaccines work by inducing immunological memory, it is imperative to understand adaptive responses in this context. In a review, LeibundGut-Landmann describes what is presently known about the role of a specific immune cell type in this process: tissue-resident memory T cells. Strategically located in peripheral tissues and especially in the mucosae, these cells trigger fast and effective responses against antigens with which the host has had previous contact. Thus, the presence of these cells in immunized individuals augments the immediate immune response beyond what is afforded by preformed innate immune effectors and could play strategic roles in antifungal immunity at barrier sites, in particular the gut, skin or respiratory mucosa. However, the biggest challenge is to devise strategies and technologies that efficiently result in memory T cells establishing residency on specific tissues after immunization, even more so when we consider the tendency of mucosal immune responses towards tolerance.

Other challenges that have so far precluded successful vaccines in medical mycology have been highlighted by Biswas in his review. Some of them are related to characteristics of these microorganisms and their interactions with the human host, such as the fact that *Candida* spp. are commensal microbes against which protective immunity is consequently very hard to achieve.

Other difficulties stem from the fact that a large proportion of patients are immunocompromised due to AIDS or one of the many therapeutic tools used in modern medicine such as stem cell transplantation, cancer chemotherapy, post-transplantation immunosuppression and broad-spectrum antimicrobials. Antifungal vaccines have also been hindered by the fact that some of these illnesses are neglected tropical diseases and that most of them tend to affect specific groups of people instead of entire populations, making their development less economically interesting for the pharmaceutical industry. Despite all these difficulties, Biswas underscores several interesting *in vitro* and *in vivo* pre-clinical studies and even an encouraging phase 1 clinical trial (2) of vaccine candidates, some of them against specific fungal pathogens and others against mycoses in general.

These pan-fungal vaccines are a possibility that stems from another study in this Research Topic (Kischkel et al.). Kischkel et al. used two different but complementary strategies to seek novel *Histoplasma capsulatum* protein epitopes that elicit robust immune responses in mice. One strategy revealed proteins that were recognized by antibodies, whereas the other showed peptides that were presented by dendritic cells to activate T cells. After identifying such immunogenic epitopes, they focused on those present in proteins that are highly conserved among different pathogenic fungal species, which could lead to cross-species immunogenicity. When these peptides were tested, they led to T cell activation and secretion of Th1- and Th17-type cytokines, a promising indication that they might enhance the kind of immune response that is protective in most systemic and mucosal mycoses.

Another genus of dimorphic fungi, *Paracoccidioides*, was the subject of a paper in this Research Topic (Silva et al.). Studies with *P. brasiliensis* have previously shown that peptides derived from the immunodominant gp43 protein can be protective in animal models (3). However, gp43 is poorly conserved in other *Paracoccidioides* species, so Silva et al. used an immunoproteomic approach to discover new candidate vaccine antigens. They were able to find immunogenic peptides that resulted in effective activation of primed T cells, a first indication that they might prove useful in future vaccines.

In contrast with the approach used in the previous two manuscripts, which sought new vaccine antigens, Rayens et al. tested whether the *Aspergillus fumigatus* homolog of a protein

they had previously found to be highly immunogenic in *Pneumocystis jirovecii* was also protective in experimental aspergillosis. Mice that were immunized with the *A. fumigatus* KEX1 protein had lower lung fungal burden, less severe pathology and increased survival after infection with *A. fumigatus* when compared with controls. Interestingly, this protection was observed even though the mice were immunosuppressed with corticosteroids or tacrolimus after the vaccination and prior to infection, a result that is very significant when considering that invasive aspergillosis happens almost exclusively in people whose immune responses are hampered.

The papers that are part of this Research Topic point to much of what we still do not know about the immunological memory to fungi, a gap that must be bridged before we can develop vaccines that successfully protect against severe fungal diseases. On the other hand, the new perspectives, and exciting experimental results presented here offer much hope towards decreasing the public health burden of the invasive mycoses.

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