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DEFENSE OF THE DOCTORAL

DISSERTATION

"Dectin-1 regulates type I and III interferon-dependent responses against *Aspergillus fumigatus* for optimal pulmonary antifungal immunity"

by

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Cancer Center G1196

ABSTRACT

One of the most prominent fungal pathogens, *Aspergillus fumigatus*, is the cause for numerous types of both acute and chronic illnesses. In an immunocompromised host, *Aspergillus* species, most commonly *A. fumigatus,* can cause severe and often fatal disease despite administration of current antifungal therapeutics. The efficacy of existing antifungal drugs is often limited due to the emergence of drug resistant fungal strains together with the inability of susceptible patients to mount a robust immune response. In this context, immunomodulation poses a promising avenue for combination therapeutics or prophylaxis. In order to develop and employ such strategies, we require a deeper understanding of the intricacies of host interactions with *Aspergillus fumigatus.*

In recent studies, we identified an essential role for type I and III interferons (IFNs) as regulators of optimal antifungal responses by pulmonary neutrophils during infection with *A. fumigatus*. We found that type I and III IFNs are necessary to promote the optimal generation of reactive oxygen species (ROS) by antifungal neutrophils. ROS is known to be an important effector response by innate immune cells for the efficient eradication of *A.fumigatus* infection. Our findings thus suggest that the antifungal response of innate cells can be modulated by type I and III IFNs.

Although various membrane and cytosolic sensors are known to regulate interferon production in response to viruses, the pathways that regulate the production of these important cytokines during fungal infection remain to be uncovered. We hypothesized that innate sensing of fungal-derived PAMPs may be involved in driving unique and novel IFN-dependent antifungal responses.

Dectin-1 is a type II transmembrane receptor expressing a single carbohydrate recognition domain. The ligands for dectin-1 are β-1,3- and β-1,6-linked glucans. These rich carbohydrate residues are found embedded in the cell walls of numerous bacteria and fungi. Although the core of the *Aspergillus* cell wall consists of β-glucans, in resting conidia these residues are shielded under proteinaceous layers of melanin and highly hydrophobic rodlets. However, when *Aspergillus* conidia begin germinating, β-glucan is available for binding by dectin-1. The downstream outcomes of β-glucan recognition include production of pro-inflammatory cytokines and reactive oxygen species (ROS), as well as expression of neutrophil chemoattractants. Our aims were to 1) determine whether exposure of β-glucan triggers IFN-dependent antifungal responses and 2) determine whether these responses are dependent on dectin-1 signaling. Our findings reveal that sensing of β-glucan by dectin-1 is an important and necessary step in activating innate immunity against *A. fumigatus* in an IFN-dependent manner. In the absence of dectin-1, these protective functions are lost, leading to mortality caused by invasive hyphal growth. Furthermore, we demonstrated that administration of exogenous IFNs is capable of restoring antifungal activity in dectin-1-deficient mice. This suggests that treatment with recombinant IFNs may be capable of boosting immune functions resulting from innate defects, such as a deficiency in pathogen sensing.