C-type lectin signaling in dendritic cells: molecular control of antifungal inflammation
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preface.
Molecular control of antifungal inflammation

Fungal pathogens represent a continuous and increasing danger to the human host. For design of novel preventive and therapeutic interventions to fungal infection, a concise understanding of the molecular mechanisms by which the immune system elicits antifungal inflammation is of utmost importance.

25 years ago, Charles Janeway, Jr. proposed the pattern recognition theory, now a fundamental framework of our modern understanding of innate immunology, which explains how a limited number of sensors expressed on innate immune cells detect invariant molecular structures associated with microbial pathogens, and instruct adaptive immune responses. Up until that time, innate immunity was seen as an unsophisticated and rather primitive part of the immune system, whereas the adaptive arm, with its B and T lymphocytes, endowed the exquisite and enormous specificity to detect pathogens and to successfully combat infection. In the years that followed, numerous pattern recognition receptor (PRR) families have been functionally characterized, and investigations have proven the fundamental and versatile role of these receptors and their signaling pathways in the control of innate and adaptive immunity. Now not only being recognized as a phenomenon intended to deal with detection of pathogens per se, but also to detect host danger in the form of damaged-self molecules. Thus, PRRs have occupied center stage in the regulation of inflammation and delineating their function and the complexity involved at the molecular level has proven an important means to obtain substantial insight in the pathophysiology of various microbial and inflammatory diseases.

While, paradoxically, fungal pathogens enabled the landmark observation that innate immune recognition is crucial for induction of host immunity in Drosophila, leading to the discovery of Toll receptors as the founding members of PRRs, we are only beginning to understand how the human immune systems responds to fungal infection, and the sophisticated mechanisms involved at the level of PRR function.
THESIS SCOPE AND OUTLINE

The research presented in this thesis, on the role of the C-type lectin receptor (CLR) family in antifungal inflammation, is aimed to identify the molecular mechanisms that govern innate and adaptive immune responses induced by dectin-1, dectin-2 and mincle, and to decipher their function during human host control— but also pathophysiology— of fungal infection.

In Chapter 1, we provide an overview of the literature in the field, serving to place our research in its proper context. CLRs expressed on dendritic cells emerge as prominent players in the control of human antifungal inflammation, and their intracellular signaling programs dendritic cell function and coordinates expression of cytokines for instruction of the adaptive immune system. Cell-mediated immunity conferred by T helper type 1 (Th1) and IL-17-producing Th17 effector cells is vital for generation of host protective immunity to fungal infection. Therefore, the series of transcriptional events underlying CLR-driven Th17 polarization were investigated in more detail in Chapter 2, where we focused on the concerted action of dectin-1 and dectin-2 in the secretion of cytokines required for Th17 polarization in response to recognition of Candida fungi. We show that transcription factor NF-κB subunit c-Rel promotes Th17 induction and since dectin-2 specifically activates c-Rel, we uncovered a distinct role for dectin-2 in shaping antifungal Th17 inflammation.

In the study described in Chapter 3, we set out to define the molecular requirements for induction of host protective Th1 immunity by CLRs, as we observed that highly virulent fungi strongly suppressed biosynthesis of Th1-polarizing cytokine IL-12. We identified transcription factor IRF1 as the pioneering factor facilitating IL12A nucleosome remodeling; our data demonstrate that the virulent fungi exploit mincle signaling for abrogation of nuclear IRF1 activities. The establishment of a very distinct role for mincle in the regulation of Th1 immunity, as well as the identification of the underlying mechanism, led to the focused investigation of the impact of mincle on the Th17 arm of antifungal inflammation. The results of these investigations are the subject of Chapter 4 and the Intermezzo section following this chapter: our data show that mincle signaling strongly amplifies Th17 polarization by modulating induction and maturation of multiple Th17 cytokines. A study on the functional aspects of type I interferons—classic antiviral immune effectors— in antifungal inflammation is described in Chapter 5, and how their induction is subject to differential modulation by CLRs but also fungi of varying virulence, signifying an important role in antifungal inflammation. Finally, in Chapter 6, our findings are shortly summarized, and
we discuss how the uncovered details on the molecular principles of CLR function and cooperation underlines their prime role in human antifungal inflammation.

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REFERENCES

