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Dermatophyte Immune Memory is Only Skin-Deep

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Abstract

A new report in this issue of *Journal of Investigative Dermatology* reveals a role for IL-17 and IFNγ, signature cytokines of Th17 and Th1 cells, in immunity to *Trichophyton benhamiae*. While there have been many recent advances in understanding host defenses against common fungi, this work illuminates not only adaptive immunity but also innate immune responses to dermatophytosis.

Introduction

The last decade has seen tremendous strides in the field of fungal immunology. Several seminal discoveries have advanced our understanding of fungal infections, particularly the identification of C-type lectin receptors as pattern recognition receptors for fungi coupled with the discovery of the Th17 subset of $CD4^+$ T cells and their importance in antifungal host defense. These advances were initially made mainly in the context of studies of *Candida albicans* infections, but have since been applied to numerous other pathogenic fungi. However, our understanding of immunity to dermatophyte infections remains comparatively limited, an important gap addressed in this manuscript (1).

Dermatophytosis is caused by pathogenic fungi that infect superficial keratinized layers of the skin. These microbes affect humans as well as other mammals, including horses, dogs, cats, and cattle. Left untreated, these fungi can cause long-lasting infections that may seriously impair quality of life. The current therapies for dermatophytosis in humans include topical or systemic administration of antifungal drugs. For animals, multiple prophylactic antifungal vaccines have been approved, though they exhibit variable success rates (2). Hence, there is a compelling need to better understand host antifungal defense pathways in the setting of dermatophytosis to develop more efficacious treatment approaches.

IL-17 and IFNγ : Mechanisms of immunity to dermatophytosis

In this issue of *Journal of Investigative Dermatology*, Marie-Pierre *et al.* (3) shed new light on the immune requirements for protection against dermatophytosis. Using mouse models and *ex vivo* approaches, the authors demonstrate that T lymphocytes constitute an integral component of defense against *Trichophyton benhamiae*. Specifically, they find that the cytokines IL-17A and IFNγ, signature cytokines of the Th17 and Th1 lineages, respectively,

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are necessary for optimal protection to this disease. Moreover, IL–17 and IFNγ exert complementary immune functions in the resolution of *T. benhamiae* infection, with IL-17A/IFNγ-double knockout mice exhibiting greater susceptibility to infection than mice lacking either cytokine alone. The authors further demonstrate the presence of fungal-specific Th1 and Th17 cells (but not Th2 cells) in skin draining lymph nodes, suggesting that *T. benhamiae* provokes a strong and specific Th1/Th17 immune signature in the skin. During infection, $CD4^+$ T cells in the lymph nodes also produced IL–22, another cytokine typically associated with Th17 immunity. Consistently, all three cytokines were upregulated in infected skin. Based on these observations, the authors conclude that Th1 and Th17 cells are crucial for dermal immunity against dermatophytes.

While IL–17 and IFNγ are clearly important, the precise mechanisms of how these cytokines drive elimination of dermatophytes was not explored in detail. IL–17 is known to signal on non-hematopoietic cells to upregulate antimicrobial peptides with potent antifungal activity, particularly β-defensins, S100A proteins and salivary histatins; additionally, some CXC chemokines induced by IL–17 have intrinsic antimicrobial activities. IL–17 also recruits neutrophils to sites of infection through induction of neutrophil-attracting chemokines, another key facet of fungal immunity (4). In oral candidiasis, IFNγ and the Th1-inducing cytokine IL–12 are dispensable for effective immunity (5, 6), but IFNγ does aid in efficient control of skin *C. albicans* infections. A recent study indicated that resolution of dermal candidiasis occurs in two steps: (i) a containment phase wherein fungi are 'walled-in' within an organized abscess to prevent spread, and (ii) an elimination phase in which proteinases digest the abscess and destroy fungi trapped within these microstructures. IFNγ was crucial for the latter stage by activating the fibrinolytic system (7). Hence, it is plausible that IFNγ might play an analogous role in controlling dermatophyte clearance. Alternatively, IFNγ polarizes macrophages to an M1 phenotype, which may also help limit dermatophytosis. Time will tell if these or additional functions mediated by these cytokines are operative in *T. benhamiae* infections.

Fungal Immunity: Adaptive versus Innate Responses

This report adds to a growing body of literature demonstrating the central importance of T-lineage cells in fortifying immune defenses of the skin. Once viewed mainly as a physical barrier, it is now well appreciated that skin harbors several different subsets of T cells that dictate antifungal immunity. In an experimental model of *Microsporum canis* dermatophytosis described recently, both $CD4^+$ and $CD8^+$ T cells were shown to be sources of IL–17 in the skin (8). In cutaneous candidiasis, skin-resident IL-17-producing $CD4^+$ T cells confer durable protective immunity (9). $CD8^+$ T cells and γδ-T cells have also been described as key cellular sources of IL–17 during dermal candidiasis (10, 11). Consistently, circulating T cells with specificity for *C. albicans* in humans are largely of the Th17 lineage (12), and humans with $CD4^+$T cell deficits due to HIV/AIDS are prone to numerous fungal infections. Thus, there is no question that T lymphocytes are central to controlling pathogenic fungi.

Accordingly, it is not surprising that, upon demonstrating roles for IL–17 and IFNg in clearing dermatophytosis, Marie-Pierre *et al.* attributed these responses to the conventional

adaptive arm of the immune system (3). However, although not emphasized, their data point to a remarkably strong contribution of innate immunity in clearing infection. *Rag2*$^{-/-}$ mice, despite lacking T and B cells, were ultimately able to clear the fungus. In immunocompetent wild-type mice, a decreased fungal load was seen in a secondary infection compared to a primary infection; nonetheless, this reduction was fairly modest, suggesting that much of the immune response is derived from an innate compartment. In this regard, IL–17 was expressed as early as three days after dermatophyte infection, far too soon to be a bona fide memory response. This swift activation of IL–17 is reminiscent of the innate type-17 responses recently described for fungal infections of barrier tissues, including the mouth, eye, lung as well as skin (10, 13–15). In the skin, γδ-T cells, a key part of the innate immune system, are the major source of IL-17 during acute *C. albicans* infections. Additionally, innate-acting "natural" Th17 cells (CD4^{+}TCRαβ^{+}) cells and ILC3s are implicated in innate control of mucosal candidiasis (16, 17), and may function analogously in the skin to control *T. benhamiae*.

Another intriguing observation in this manuscript worthy of mention is that secondary-challenged *Rag2*$^{-/-}$ mice displayed a lower fungal burden than primary infected Rag2$^{-/-}$ counterparts at some early time points. This protection during reinfection in absence of an adaptive immune system is suggestive of 'trained immunity', a relatively new concept whereby immunological 'memory' of previously-encountered antigens is imprinted epigenetically in monocytes (18). Unconventional immune memory has also been described in dermal epithelium, where epithelial stem cells show heightened responses to secondary challenges to stressors (19). Hence, a primary dermatophyte infection may prime keratinocytes and monocytes to respond more potently during re-infections that account for much of the recall immune response.

Questions and Future Directions

There are other questions raised by these studies. Whereas IL–17A is clearly important, the role of the related cytokine IL–17F, also made by adaptive and innate Type 17 cells, remains unknown. IL–17F certainly contributes to fungal clearance in both mice and humans in oral mucosal candidiasis (20–22). Surprisingly, mice with a single IL–17A deficiency do not exhibit strong susceptibility to oropharyngeal candidiasis, and humans taking anti-IL-17A biologics for autoimmune disease are similarly not strongly prone to the disease (4). An inference from the *Rag2*$^{-/-}$ infection experiments is that T cells are important for host defense, but these mice also lack functional antibody-producing B cells, which might add an additional layer of protection against repeated dermatophyte challenges (23). Finally, cross-talk between sensory neurons and the immune system was recently shown to be crucial for clearance of dermal *C. albicans* infections; the neuropeptide calcitonin gene-related peptide (CGRP) stimulates dermal DCs to produce IL–23, which in turn activates γδ-T cells to express IL–17 and clear the fungus (24). The possible contribution of sensory neurons in instigating anti-dermatophyte responses was not addressed in this study, but would be an intriguing avenue of investigation.

In summary, this work represents a notable advancement in the field of fungal immunology, illuminating host defenses to a superficial fungal infection that impacts a large portion of the

world population. The study reinforces the idea that host mucosal and barrier surfaces are equipped with sophisticated immune defense networks that work in a synchronized manner to counter microbial pathogens such as *Trichophyton benhamiae* and limit spread to other distal sites. These mechanistic insights into the workings of the dermal immune system are foundations that will be needed in the pursuit of antifungal vaccines, none of which exist to date.

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