

New insights into immunity to skin fungi shape our understanding of health and disease

Fiorella Rucht^{1,2}  | Salomé LeibundGut-Landmann^{1,2} 

¹Section of Immunology, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland

²Institute of Experimental Immunology, University of Zürich, Zürich, Switzerland

Correspondence

Salomé LeibundGut-Landmann, Section of Immunology, Vetsuisse Faculty, University of Zürich, Winterthurerstrasse 266a, Zürich 8057, Switzerland.
Email: salome.leibundgut-landmann@uzh.ch

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Abstract

Fungi represent an integral part of the skin microbiota. Their complex interaction network with the host shapes protective immunity during homeostasis. If host defences are breached, skin-resident fungi including *Malassezia* and *Candida*, and environmental fungi such as dermatophytes can cause cutaneous infections. In addition, fungi are associated with diverse non-infectious skin disorders. Despite their multiple roles in health and disease, fungi remain elusive and understudied, and the mechanisms underlying the emergence of pathological conditions linked to fungi are largely unclear. The identification of IL-17 as an important antifungal effector mechanism represents a milestone for understanding homeostatic antifungal immunity. At the same time, host-adverse, disease-promoting roles of IL-17 have been delineated, as in psoriasis. Fungal dysbiosis represents another feature of many pathological skin conditions with an unknown causal link of intra- and interkingdom interactions to disease pathogenesis. The emergence of new fungal pathogens such as *Candida auris* highlights the need for more research into fungal immunology to understand how antifungal responses shape health and diseases. Recent technological advances for genetically manipulating fungi to target immunomodulatory fungal determinants, multi-omics approaches for studying immune cells in the human skin, and novel experimental models open up a promising future for skin fungal immunity.

KEYWORDS

Candida, dermatophytes, fungal infection, inflammatory skin conditions, *Malassezia*, mycobiome, skin immunity, type 17 immunity

1 | INTRODUCTION

The skin is constantly exposed to a plethora of chemicals, environmental antigens, and microorganisms including their metabolites. It provides vital barrier functions and immune surveillance to protect our body from these potentially threatening insults.^{1,2} An intricate crosstalk between diverse subsets of highly specialized immune and non-immune cells in epidermis and dermis sustain these protective mechanisms and prevents pathology by

distinguishing commensal microbes colonizing the skin from harmful pathogens.³

The fungal kingdom represents an understudied class of skin resident microorganisms. While a large body of studies has focussed on dissecting the bacterial microbiome of the skin in health and disease and across ethnicities and gender, relatively little is known about the fungal compartment, the mycobiome, of the skin.

The most abundant fungal genus colonizing the healthy human skin is *Malassezia* with a minor contribution of *Candida* and other

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fungi.⁴ Besides their primary role as commensals in steady state, *Malassezia* spp. have been implicated in several inflammatory and non-inflammatory skin pathologies.⁵ Moreover and importantly, infectious diseases caused by various pathogenic skin fungi are responsible for the vast majority of mycotic diseases worldwide.⁶ Only recently, we started to learn about the immune mechanisms raised against skin fungi mediating host protection.

This review focuses on the current knowledge of interactions of skin fungi with the host in health and disease with particular focus on the commensal yeast *Malassezia*. It discusses important discoveries in cutaneous antifungal immunology and highlights important open questions in the field.

2 | THE SKIN MYCOBIOME

Since the advent of high throughput sequencing technologies, the field of mycobiome research has experienced a steep rise. The molecular methods enabled mapping a detailed and more unbiased picture of the composition and relative abundance of skin resident fungi compared to what was possible with traditional culture-based approaches.^{7,8} Still, fungal sequences remain underrepresented on the skin, constituting less than 5% of the whole cutaneous microbiome.⁴ Considering the much larger volume of fungi relative to most bacterial species, they offer however more biomass than bacteria to interact with the host.⁹ In comparison to the bacterial communities on the skin, the mycobiome displays a surprisingly low diversity and is largely dominated by a single fungal genus, i.e. *Malassezia*. Until today, 20 species of *Malassezia* have been reported across a wide range of different hosts including diverse pet and farm animals, but even aquatic animals like seals and sea lions.^{10–12} *M. pachydermatis* was the first species to be described almost 100 years ago.¹¹ Ten of the 20 known *Malassezia* species have been identified in humans with *M. restricta* and *M. globosa* being the most abundant representatives of the genus and *M. sympodialis* also being frequently detected but at lower levels.^{7,10}

Colonization of the human skin by *Malassezia* starts directly after birth.¹³ During childhood fungal diversity is greater than in adulthood with dermatophytes being readily detected. This diversity decreases after puberty with a dominance of *Malassezia* establishing, likely due to increased activity of sebaceous glands post-puberty.¹⁴ Comparing absolute *Malassezia* abundance between different body sites is hampered by the method employed for sampling, which can introduce a large bias. Relative to bacteria and viruses, the external auditory canal shows the highest abundance of *Malassezia*.¹⁵

The feet represent the only external body site displaying large fungal diversity comprising *Candida*, *Cryptococcus*, and *Aspergillus* species, and subclinical colonization by dermatophytes. In turn, *Malassezia* constitutes less than 20% of the mycobiome on feet.⁸ Interestingly, the skin mycobiome of healthy adults is very stable over time whereby the composition varies more between different skin sites at a given time point than within a specific site at different time points.⁷ Under pathological conditions, however, the relative abundance of

individual fungal genera and species can vary. Meanwhile, dysbiosis may contribute to dysregulation of potentially protective host-microbiome interactions while interactions with the components of the skin microbiota may worsen the disease.

Although the skin mycobiome composition varies between skin sites and between healthy and diseased skin, *Malassezia* almost always dominates over any other fungal genus, while they are rarely found in other barrier tissues, and if so at low levels. The predominance of a single fungal genus raises the question what distinguishes the skin from other body sites and which features make it an attractive niche for skin-resident fungi.

3 | NICHE REQUIREMENTS OF SKIN-RESIDENT FUNGI

While the skin forms a protective barrier against physical, chemical, and microbial insults, this barrier is not impermeable with many glands and hair follicles found embedded within the skin. For many skin-resident fungi, appendages such as hair follicles or sebaceous glands serve as special niche since they are nutrient-rich and provide a confined and protected space for growth. They, thus, serve as important hubs of interaction for microbes and microbe-derived products with the host.¹ Skin fungi like *Malassezia* are specialized in utilizing lipids as a main nutrient source. *Malassezia* secretes several lipases and phospholipases that break down essential lipids from the host to make them available as nutrients since the lipophilic fungus lacks its own fatty acid synthase for lipogenesis.¹⁶ On the other hand, dermatophytes are keratinophilic and, in addition to lipases, possess keratinases to decompose keratin from the stratum corneum of the skin, from nails and hair to gain access to amino acids and short peptides.¹⁷ Some of these fungal catabolic enzymes may also act as virulence factors under disease conditions by promoting skin barrier disruption to establish infection and cause pathology, as discussed in a later section.

4 | FUNGAL SKIN INFECTIONS

Diseases caused by skin fungi range within the 10 most prevalent diseases worldwide with an estimated 20%–25% of the worldwide population being affected by superficial fungal infections.^{18,19} The most common fungal skin infections are those caused by dermatophytes, which in humans most frequently manifest as tinea capitis, tinea pedis or onychomycosis. Among the around 50 species of dermatophytes that have been described, *Trichophyton* and *Epidermophyton* species act as pathogens in humans.²⁰ Besides anthropophilic dermatophytes, zoophilic dermatophytes are a common cause of fungal skin infections in animals, especially in cattle and in companion animals, and they exhibit a significant zoonotic potential.²¹

Children with a naïve immune system, elderly with a weakened immune system and immunocompromised individuals such as

transplant, cancer, and AIDS patients are generally at higher risk for developing mucocutaneous mycoses and they are affected by a broader range of fungal pathogens. This highlights the role of the immune system in preventing fungal overgrowth and tissue invasion. As such, mucocutaneous candidiasis is common in patients undergoing immunosuppressive therapies in the context of cancer or transplantation and in people with acquired or inherited immune defects such as in AIDS patients or in those with genetic defects in specific T helper cell-associated genes.²² This demonstrates a particular role of T cell-mediated immunity for antifungal control in barrier tissues. The relevance of an intact skin barrier for protection from fungal infections is illustrated by several fungal pathogens that take advantage of injured skin sites to breach the skin barrier. As such, skin infections by *Candida* spp., mucorales, *Fusarium* spp. or *Aspergillus* spp. are a frequent and serious problem in burned patients.^{23,24} These fungi and others are also agents of complication in chronic wounds contributing to impaired healing such as in diabetic foot ulcers.²⁵ Chromoblastomycosis, eumycetoma and sporotrichosis can occur when fungi penetrate the skin through accidental (traumatic or via surgical) implantation to cause subcutaneous lesions, if not timely treated.^{26,27}

The common skin commensal yeast *Malassezia* has also been associated with several pathological conditions of the skin including dandruff, pityriasis versicolor, seborrheic dermatitis and atopic dermatitis. A causal link between *Malassezia* and some of these diseases has been established based on the observation that antifungal therapy can relieve the symptoms with improvements in dandruff and seborrheic dermatitis after antifungal treatment.²⁸ Still, in case of atopic dermatitis, the role of *Malassezia* in disease pathogenesis remains less clear (as discussed in a later chapter).

Fungal infections of the skin are usually mild and treatable, albeit full resolution of infection can be lengthy and tedious. In immunocompromised individuals, therapy of fungal infections tends to be more difficult, and the course of disease is often chronic or recurrent. A challenge to successful antifungal therapy remains the availability of only a limited number of pharmacological drugs and the rise of antifungal resistance against available compounds.

5 | HOST DEFENCE MECHANISMS OF THE SKIN

While fungal infections represent an increasing medical challenge, they remain the exception despite the constant exposure to fungi in the environment and the microbiota. This raises the question how skin fungi are held in check during steady state for maintenance of stable homeostasis and, on the other hand, under which circumstances can fungal skin pathologies still occur. The mammalian skin is equipped with a complex array of passive and unspecific defence mechanisms as well as targeted cellular responses that cooperate and complement each other for protective antifungal immunity.

5.1 | The skin barrier

Like a shield, the skin protects the body from external insults by mounting a physical barrier and providing a matrix for an intricate immunological network. Constant renewal of the epithelium and wound healing in the aftermath of an injury are elementary processes that ensure the maintenance of this shield.

The outermost skin barrier, the stratum corneum, consists of dead keratinocytes, keratins and lipids that provide a hydrophobic environment important for water retention. Underneath, in the stratum granulosum, the tight linkage of keratinocytes via tight junctions provides a second protective layer. Finally, the innermost layer of the epidermis is formed by the stratum basale harbouring stem cells essential for keratinocyte renewal. The dermis is structured by a scaffold of extracellular matrix proteins, is innervated by terminal nerve fibres, and vascularized to allow entry of inflammatory immune cells from the circulation in case of infection and inflammation.¹

Besides mediating physical protection from fungi, epithelial cells are competent in recognizing fungi, and even more in discerning different states of fungal virulence in response to which they initiate an immunological cascade.²⁹ Epithelial cells are vital producers of antimicrobial peptides exerting fungistatic or fungitoxic activities. Skin resident immune cells embedded in the epidermis and in the dermis ensure efficient immunosurveillance of skin fungi to prevent their overt growth or tissue invasion by directly sensing fungi and fungal products via pattern recognition receptors and by responding to keratinocyte-derived alarmins.²⁹ Langerhans cells forming a cellular network in the epidermal layer were shown to facilitate surveillance of *C. albicans* in their function as antigen-presenting cells.³⁰ Among the tissue-resident immune cells in the dermis are macrophages, mast cells, and several subsets of dermal dendritic cells as well as $\gamma\delta$ and $\alpha\beta$ T cells.¹ While the primary role of these cells is in maintaining immune homeostasis during commensalism, they are critical for mounting protective immunity against tissue-invading fungi including primary fungal pathogens by contributing to cytokine production and antimicrobial effector mechanisms.³¹ In addition, circulating immune cells are rapidly recruited to the skin upon fungal invasion, which is typically accompanied by the release of host alarm signals in the damaged tissue, to support the local immune forces (Figure 1).

5.2 | Fungal recognition in the skin

Recognition of fungi in the skin is essential for the induction of an effective antifungal immune response. This process is mediated by diverse pattern recognition receptors (PRRs) expressed on myeloid and epithelial cells that sense conserved structures of the fungal cells.^{31,32} C-type lectin receptors (CLRs) bind fungal cell wall carbohydrates and initiate a signalling pathway via the tyrosine kinase Syk and the adaptor Card9 that activates innate immunity and couples to the adaptive immune system for T cell activation.³³ PRRs on antigen-

presenting cells that migrate to the skin-draining lymph nodes are pivotal in T cell priming. Together with other environmental/milieu factors, they promote MHC-mediated antigen presentation and co-stimulation, and they induce the production of polarizing cytokines. The latter depends qualitatively on the type of PRR engaged and allows establishing a protective T cell response.³⁴ As such, Card9 plays a pivotal role in the induction of T helper 17 (Th17) immunity against fungi as evidenced by individuals with loss-of-function mutations in CARD9 suffering from chronic mucocutaneous candidiasis and displaying an impaired Th17 response.^{35–37} The relevance of Card9 for induction of antifungal Th17 immunity was further confirmed in mouse models of *C. albicans*, *C. auris* and *M. pachydermatis* infection.^{33,38,39} Similarly, congenital defects in CARD9 are implicated in several fungal infections starting from the skin and subsequently

disseminate to secondary tissues, such as invasive *Exophiala* infections and deep tissue dermatophytosis.^{35,40}

While extensive studies have been performed to dissect the relative contribution of individual CLRs and other classes of PRRs to the host response against *C. albicans*, the situation remains less clear for other skin fungi. In the following, we summarize the current state of knowledge about innate recognition of the major skin fungus *Malassezia*.

While Mincle was initially shown to bind selectively to *Malassezia* spp. and Mincle deficiency abrogated the cytokine response of myeloid cells to the fungus,⁴¹ both Mincle and Dectin-2 have later been shown to complementary bind to lipophilic and hydrophilic structures of *Malassezia*, respectively.⁴² In bone marrow-derived dendritic cells, Dectin-2 enhanced the production of reactive oxygen species (ROS)

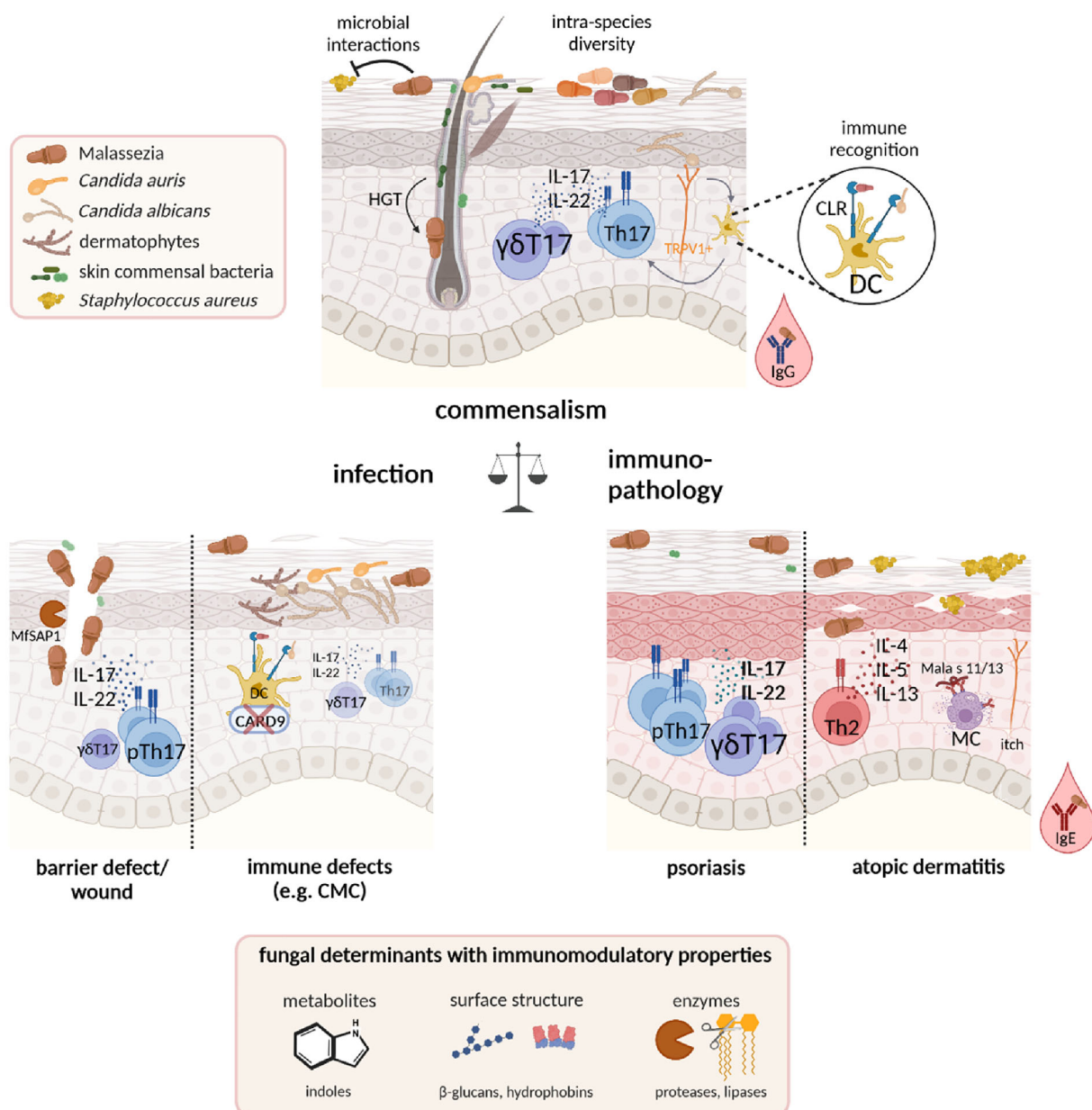


FIGURE 1 Legend on next page.

for *Malassezia* killing after phagocytosis,⁴³ providing further evidence for a role of Dectin-2 in *Malassezia* recognition. Moreover, Dectin-1 blockade resulted in impaired *M. furfur*-induced cytokine secretion by human dendritic cells.⁴⁴ However, in a mouse model of *Malassezia* skin colonization, Dectin-1, Dectin-2 and Mincle appeared to be redundant for overall fungal control.³⁸ The relative role of distinct CLRs during *Malassezia* commensalism versus pathogenicity thus remains to be dissected. Similarly, the cell types in which the receptors act remain to be defined. While CLRs are traditionally associated with the expression on myeloid cells including dendritic cells, macrophages and neutrophils, Dectin-1 has also been found expressed by human keratinocytes.⁴⁵ Besides CLRs, NOD-like receptors have been found engaged in response to *Malassezia*. As such, NLRP3-mediated inflammasome induction was reported in myeloid cells upon exposure to *M. furfur*.^{43,44}

Toll-like receptors (TLRs) are another class of PRRs with a pivotal role in fungal recognition. TLR2-mediated recognition of *Malassezia* by keratinocytes triggers an inflammatory response by upregulation of antimicrobial peptides and inflammatory cytokines such as IL-8 which allows for the recruitment of neutrophils and other granulocytes.⁴⁶ Furthermore, mice deficient in MyD88, the downstream adaptor of most TLRs and IL-1 family receptors, showed delayed clearance of *Malassezia* in an animal model of skin colonization.³⁸ Furthermore, protease-activated receptors (PARs) have been shown to sense fungal proteases as well as tissue injury caused by fungal virulence factors and modulate TLR-induced immune responses.⁴⁷

Intracellular RNA sensors are potentially involved in recognizing *Malassezia* and inducing the production of type I interferon in response to fungal strains containing a mycovirus.^{48,49} This adds an additional level of complexity. Mycoviruses may therefore affect how the fungus is recognized, influence the quality of the response that is mounted and thereby modulate the pathogenicity of the fungus.

Moreover, the presence of mycoviruses led to transcriptomic changes in *Malassezia* influencing metabolic functions and stress-resistance within the yeast cells.⁴⁸ Studying the presence of mycoviruses in fungal strains isolated from specific pathogenic skin conditions versus healthy skin and their contribution to the pathogenicity of the fungus promises to advance our understanding of *Malassezia*-mediated pathologies.

Beyond fungal recognition via bona fide PRRs, epithelial cells can also sense fungi via receptors such as EGFR and EphA2, whose primary functions are in cellular processes/tissue homeostasis rather than microbial recognition.⁵⁰ Epithelial cells can further distinguish between different states of fungal virulence, as has been shown in case of *C. albicans*.⁵¹ Whether *Malassezia* and other skin fungi interact via similar mechanisms with epithelial cells remain to be established.

5.3 | Type 17 immunity in antifungal defence

T cell responses directed against skin fungi display predominantly a type 17 profile in line with IL-17's well-known role in defence against fungi and other extracellular microbes in barrier tissues.⁵² This has first been evidenced by *C. albicans*-reactive T cells that display a strong Th17 profile in the peripheral blood of healthy individuals primed in response to commensal fungi.⁵³ *C. albicans*-reactive Th17 cells are evidenced in the skin as well.⁵⁴ Healthy individuals bear Th17 cells directed against a large spectrum of other commensal and environmental fungi, among which *Malassezia*-reactive Th17 cells feature prominently in line with the abundance of this commensal yeast on the entire body surface.⁵⁵ These findings are complemented by experimental studies demonstrating a relevant role of IL-17 cytokines in protection against *C. albicans*,²⁹ *Candida auris*,³⁹ *Malassezia* spp.,³⁸ and dermatophyte⁵⁶ skin infections. IL-17 cytokines mediate

FIGURE 1 Skin fungi in cutaneous health and disease. The immunity to skin fungi is context-dependent with fungal factors being able to modulate the host immune response and influence health during commensalism and disease settings during infection and immunopathology. Commensal fungi are recognized by dendritic cells (DCs) primarily via C-type lectin receptors (CLRs) or by TRPV1⁺ neurons that facilitate recruitment of IL-17A-producing $\gamma\delta$ ($\gamma\delta$ T17) and initiate priming of a fungus-specific adaptive immunity including IgG detectable in the blood as well as local and systemic T helper 17 cells (Th17). $\gamma\delta$ T17 and Th17 contribute to keeping the fungi in check during commensalism by IL-17A and IL-22 secretion. Furthermore, the cutaneous microbiota interacts with skin fungi in several ways, including gene acquisition via horizontal gene transfer (HGT) or *Malassezia*-mediated inhibition of *Staphylococcus aureus* biofilm formation. Besides the diversity of different fungal species residing on the skin including *Malassezia* spp. and *Candida* spp., analyzing intra-species diversity may shed light on pathology-associated colonization. Upon breaching of the epithelial barrier or tissue entry via wounds, skin fungi can penetrate into deeper tissue layers causing IL-17-mediated inflammation and further damage. The secreted aspartyl protease 1 of *M. furfur* (MfSAP1) can interfere with wound healing. In case of innate immune deficiencies involved in IL-17 induction such as CARD9, the downstream adaptor of CLR signalling, cutaneous fungi cannot be controlled properly. Fungal overgrowth and chronic mucocutaneous candidiasis (CMC) result as a consequence. On the other hand, excessive or pathogenic IL-17-production can cause chronic inflammation and skin tissue remodelling as observed in psoriasis. Aberrant antifungal type 2 responses including fungus-specific Th2 and IgE are recognized in atopic dermatitis (AD). While AD flares are associated with a leaky skin barrier and overgrowth of *S. aureus*, *Malassezia*-specific type 2 responses are correlated with AD disease severity. Th2-derived cytokines such as IL-4, IL-5 and IL-13 contribute to neuron activation and itching as well as granulocyte recruitment into the skin including mast cells (MCs) bearing IgE on their surface. *Malassezia*-derived allergens, for example, Mala s 11 and Mala s 13, can act as auto-antigens due to cross-reactivity with host proteins, henceforth aggravating disease. Fungal factors can modulate the host immune response during steady-state and inflammation. Fungal metabolites and enzymes can act as skin irritants or interfere with the host's skin barrier function. Conserved structures of the fungal cell wall such as β -glucans, which are recognized by CLRs, are key factors in immune recognition and initiating protective antifungal responses. Other fungal surface structures such as hydrophobins found on dermatophytes assist in evasion of immune recognition by the host. The figure was created using [Biorender.com](https://biorender.com).

antifungal defence by IL-17 receptor signalling in epithelial cells and fibroblasts, which enhances the production of antimicrobial peptides, some of which have been shown to be essential for fungal control in vivo.^{52,57,58} Moreover, IL-17 signalling holds a host protective role in maintaining skin barrier integrity, facilitating tissue repair and wound healing, both of which being critical for well-controlled cutaneous fungal colonization.⁵⁹ While IL-17 can also enhance the expression of neutrophil-recruiting chemokines,⁶⁰ promoting the neutrophil response is not a major effector function of IL-17 during fungal commensalism as neutrophils do not enter colonized tissues during steady state despite the continuous activity of Th17 cells.⁶¹ The protective effects of IL-17 are at least in part shared with those of IL-22, as Th17 directed against skin fungi often co-produce IL-22,^{38,55,62} and IL-17 receptor expression was proposed to be enhanced by IL-22 in a model of oral candidiasis.⁶³

Beyond CD4⁺ T cells, other lymphoid cells contribute to the overall IL-17 response to commensal fungi including CD8⁺ T cells, dermal $\gamma\delta$ T cells and TCR-negative innate lymphoid cells (ILCs).^{29,38} While the different IL-17 producing cell types respond to the same activating/polarizing cytokines IL-1, IL-6 and IL-23, they exhibit different response dynamics with innate lymphoid cells type 3 (ILC3) and $\gamma\delta$ T cells being activated more rapidly compared to CD4⁺ and CD8⁺ T cells. In experimental models that represent a primary encounter of the immune system with the fungus, dermal $\gamma\delta$ T cells were shown to be essential for limiting fungal growth,^{29,38} similarly to what was shown for skin bacteria such as *S. aureus* and *Corynebacterium* spp.⁶⁴ while in other tissues $\gamma\delta$ T cells play a redundant role for antifungal IL-17 immunity.^{65,66} IL-17 production by human $\gamma\delta$ T cells in response to commensal fungi has been documented as well. In untreated HIV⁺ patients with *Candida* co-infections, IL-17-producing $\gamma\delta$ T cells were postulated to compensate, at least in part, for the diminished CD4⁺ T cells.⁶⁷ CD8⁺ T cells also produce IL-17 in response to skin fungi,^{30,56,68} although they have not been studied in detail in contrast to CD8⁺ T cell responding to *S. epidermidis* in the skin.⁶⁹

The cytokines driving activation/polarization of type 17 immunity, commonly IL-23, IL-6 and IL-1, are primarily derived from tissue-resident myeloid cells (including antigen-presenting cells in case of adaptive T cell priming) in response to direct sensing of the fungus by these cells. Other skin cells, especially epithelial cells, may also contribute to the production of IL-17-inducing cytokines. This was shown in the context of an acute *C. albicans* infection model with a virulent strain of *C. albicans* that elicits massive cellular damage and thereby triggers the release of IL-1 from the damaged cells.⁷⁰ The neuronal system has also been implicated in the initiation of antifungal type 17 immune responses in the skin, as revealed in the context of cutaneous candidiasis.⁷¹ Sensory neurons in the skin of experimentally infected mice were found to directly sense *C. albicans* and initiate production of the sensory neuropeptide Calcitonin Gene-Related Peptide (CGRP). CGRP in turn induced the production of IL-23 by CD301b⁺ dermal dendritic cells and thereby instructed $\gamma\delta$ T cells for IL-17-production,^{71,72} reminiscent of findings in the context of psoriasis.⁷³ Remarkably, TRPV1⁺ neuron activation was sufficient to elicit a local type 17 immune response against *C. albicans*, independently of

tissue damage or pathogen-associated products.⁷² The role of pathogen recognition and the importance of non-immune cells to initiate a functional immune response is an emerging field of research that connects neuroimmune interactions in the context of host defence and inflammation.

5.4 | Long-term IL-17-mediated protection against skin fungi

To ensure long-term homeostatic immunity against commensal fungi that persist on the skin and to guarantee efficient protection against re-infection with environmental fungi to which we are continuously exposed, long-lived antifungal mechanisms are required. T cells excel by virtue of their capacity to form long-lived memory. As such, *C. albicans*-reactive Th17 cells detected in human blood and skin display a memory phenotype.^{54,74,75} Long-lasting T cell immunity against dermatophytes, a common skin fungus in livestock and pet animals, can be assessed by skin prick testing. Affected animals that had prior been infected with or vaccinated against *Trichophyton* show a delayed-type hypersensitivity reaction indicating reactivation of pre-existing dermatophyte-specific memory T cells.⁷⁶ In the human skin, *C. albicans*-specific Th17 cells further expressed markers characteristic of tissue-resident memory T cells (TRMs).⁵⁴ Likewise, in a model of *C. albicans* commensalism characterized by persistent fungal colonization in the murine oral mucosa, *C. albicans*-specific Th17 cells exhibit tissue-residency.⁷⁷

Similar to Th17 cells, IL-17-producing $\gamma\delta$ T cells have been suggested to establish long-lasting memory in settings of IL-17-mediated skin pathologies with enhanced reactivity to secondary challenge and exhibition of memory-like phenotypic characteristics.^{78,79} Whether $\gamma\delta$ T cell-mediated recall responses are driven by a specific antigenic responsiveness or are broadly reactive has not been addressed. $\gamma\delta$ T cells establishing memory-like features is in line with the concept of trained immunity that has gained attention in recent years.⁸⁰ Whether $\gamma\delta$ T cells activated in response to fungi establish memory for enhanced responsiveness to persisting or recurring fungal exposure, as it has been shown in the gastro-intestinal tract for protection against *Listeria*,⁸¹ remains to be examined.

6 | SKIN FUNGI DRIVING INFLAMMATION AND PATHOLOGY

6.1 | Dysregulated adaptive antifungal immunity driving immunopathology

While type 17 antifungal immune responses are required for protection against a broad range of organisms, including both commensal and pathogenic fungi, aberrant type 17 responses can confer inflammation and pathology (Figure 1). Overt production of IL-17 drives the pathogenesis of autoimmune disorders, such as psoriasis. This is highlighted by the therapeutic efficacy of IL-17 targeting antibodies in

this disease.⁸² The antigenic specificity of disease-promoting IL-17-producing T cells, however, remains currently unclear. It is conceivable, though, that disease pathogenesis relies on microbiota-induced, originally host protective IL-17-producing T cells that acquire pathogenic properties in predisposed hosts or as a result of environmental insults.⁸³ As such, *C. albicans*-specific Th17 cells have been shown to promote pathology, even in distant organs such as the lung, which itself is not readily colonized by *C. albicans*. This was observed in both human patients with airway inflammation such as acute allergic bronchopulmonary aspergillosis and in mice during experimentally-induced airway inflammation.^{55,84} Mechanistically, *C. albicans*-induced Th17 cells were proposed to cross-react with *Aspergillus* in the lung, which harbours several antigens that are conserved between the two fungi.⁵⁵ Skin T cells emerging after cutaneous association with a range of different fungi in an imiquimod-induced model of psoriasis, including *C. albicans*, *M. furfur* and the dermatophyte *T. mentagrophytes*, could aggravate psoriasis via IL-17 mediated pathology.⁶⁸

That T cells directed against skin fungi can promote pathology via cross-reactivity has further been proposed for *Malassezia*-induced T cells in the context of atopic dermatitis (AD). Based on conserved structures between the *Malassezia* antigen Mala s 13 and the human protein thioredoxin, T cells from the blood and skin of AD patients directed against Mala s 13 were fully cross-reactive with human thioredoxin.⁸⁵ Another autoallergen is presented by the human manganese superoxide dismutase (MgSOD) that was demonstrated to share antibody epitopes with the *Malassezia*-derived MgSOD characterized as Mala s 11.⁸⁶ Furthermore, sensitization to Mala s 11 was positively correlated with disease severity.⁸⁷ Although AD is generally thought to be a type 2-mediated disease and AD patients prominently bear *Malassezia*-responsive Th2 cells, a subset of Mala s 13 cross-reactive T cells also produce IL-17 and IL-22.⁸⁵ This is in line with the notion that IL-17 may contribute to disease in some patient groups⁸⁸ and that Th17 immunity against *Malassezia* can exacerbate cutaneous inflammation in a model of AD.³⁸ Besides T cells, the antibody response against *Malassezia* is dysregulated in AD with *Malassezia*-specific IgE detected in about 50% of the patients.⁸⁹ What leads to the dysregulated T cell and antibody response in AD remains currently unclear. Finally, whether the dysregulated *Malassezia*-specific Th2 cells and IgE play an active role in disease pathogenesis or rather are a bystander consequence in type 2 polarized allergic skin is unknown.

6.2 | Fungal factors modulating the host to promote skin inflammation and pathology

In addition to T-cell and antibody-mediated mechanisms of fungi-associated pathologies, skin fungi can contribute to inflammatory skin disorders by releasing bioactive molecules that modulate the fungus-host interaction, independently of the adaptive immune system. Fungal proteases and metabolites have, indeed, been observed to promote inflammation and cause skin barrier disruption. One of the first putative virulence factors that was discovered in *Malassezia* is

Malassezin, a metabolite with the potential to induce apoptosis in keratinocytes as characterized in pityriasis versicolor patients.⁹⁰ Several other metabolites and enzymatic proteins have been linked to disease exacerbation in this *Malassezia*-associated pathology¹⁶ and in the context of chronic wounds.^{91,92} An example of such an enzyme is the Secreted Aspartyl Protease 1 of *M. furfur* (MfSAP1) that potently degrades diverse extracellular matrix proteins of the human skin. Thereby, MfSAP1 may interfere with wound healing processes as suggested from results obtained with an in vitro skin model.⁹² Secondary metabolites of *M. furfur* such as indolic compounds with immunomodulatory effects have been identified in the context of seborrheic dermatitis and dandruff.^{93,94} Finally, *Malassezia* hyphae were observed in lesions of pityriasis versicolor patients, and, reminiscent of *C. albicans*, filamentation was proposed as an additional virulence factor of *Malassezia*.¹⁶

Virulence factors of dermatophytes include enzymes involved in keratin degradation like hydrolases, endoproteases and exoproteases that have been implicated in tissue damage, host invasion and subsequent inflammation.¹⁷ Additional dermatophyte virulence factors allow for modulation of or evasion from the host immune response as in case of hydrophobins, which can mask fungal recognition by neutrophils.⁹⁵

The most well-studied skin fungal virulence factors driving inflammation and pathology in the host are those of *C. albicans*.⁹⁶ Discussing them in detail here would exceed the scope of this review. One of the factors that gained much attention over the past years is the peptide toxin candidalysin,^{97,98} which not only is critical for *C. albicans* pathogenicity but also for eliciting inflammation in barrier tissues and driving immunopathology, as in case of vulvovaginal candidiasis.⁹⁹

As in case of candidalysin and many other *C. albicans* virulence factors, genetic approaches have been instrumental for establishing their role as modulators of the host immune system and their significance in pathogenicity. Genetic manipulation has become available for dermatophytes and more recently for *Malassezia*. *Agrobacterium tumefaciens*-mediated transformation enables targeted and random insertion mutagenesis as well as the insertion of reporter genes in several species of *Malassezia* and *Trychophyton*.^{100,101} The availability of these genetic tools promises to advance the understanding of fungal determinants involved in fungal-host interactions and exploring their relevance in homeostatic and/or pathological conditions.

6.3 | Microbial interactions in the skin shaping cutaneous pathological conditions

While skin fungi can significantly impact skin homeostasis and drive inflammation in the host by directly acting on the skin or via aberrant antifungal T and B cell responses, as elaborated above, their tight interactions with other members of the skin microbiota further impact the fungus-host interplay. Large-scale sequencing studies have shed light on the complexity of fungi-fungi interactions and interkingdom interactions between bacteria and fungi in healthy skin and under pathological conditions characterized by dysbiosis.⁴ Meanwhile, only a very limited number of studies have mechanistically investigated the

functional consequences of changes in the microbial communities on the skin and how they shape cutaneous immune responses and pathologies.^{25,102} Dysbiosis of the skin microbiota is associated with skin disorders such as AD. Lesional skin of AD patients features increased diversity in the mycobiome with a concomitant decrease in the abundance of *Malassezia* spp.,^{31,103} as well as a dominance of *Staphylococcus aureus*^{104,105} in the bacterial compartment. *S. aureus* is widely accepted as a driver of disease pathogenesis in AD. In this context, it is of interest that a secreted aspartyl protease of *M. globosa* (mgSAP) can restrict the formation of *S. aureus* biofilms.¹⁰⁶ Thus, interkingdom interactions between *M. globosa* and *S. aureus* mediated via MgSAP can presumably counteract *S. aureus* overgrowth associated with AD flares. Another recent example of inter-microbial interactions shaping the skin homeostasis involves *Candida auris*, a highly resistant fungal species that has become a public health concern. Skin colonization and nosocomial transmissions pose a serious risk for disseminated infections with high mortality rates in susceptible individuals.¹⁰⁷ Sequencing of the skin microbiomes of residents of a nursing facility revealed negative associations of specific *Staphylococcus* and *Corynebacterium* species with *C. auris* colonization on the skin.¹⁰⁸ Furthermore, *C. auris*-carriers showed diminished colonization with *Malassezia* spp. while high diversity of *Malassezia* colonization appeared to be a protective feature limiting *C. auris* invasion.¹⁰⁸

A different level of interaction within the microbiota is facilitated by the exchange of genetic material between skin-resident microbes. An example of such an event is provided by *Malassezia*, which acquired selected genes from bacteria that share the same niche via horizontal gene transfer events involved in oxidative stress response such as flavohaemoglobin allowing for increased nitrosative stress resistance.^{109,110} Such inter-kingdom interactions drive the evolution of microbes and facilitate functional adaptation to the host environment while, at the same time, they have the capacity to determine commensal or pathogenic states. While fungal dysbiosis is associated with various pathological conditions, understanding the consequences for health and disease of these multi-layered interactions of skin microorganisms among each other and in the interplay with the host poses a major future challenge. Results from future efforts towards that direction promise to inform about the benefit of pre- and probiotics for promoting skin homeostasis or about the feasibility of targeting specific fungal factors as disease-preventive approaches.

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

The host response to skin fungi is highly context-dependent. Skin-resident fungi are in a constant crosstalk with other members of the microbiota as well as with the immune system and other cutaneous cells such as epithelial cells and even neurons. Studies monitoring the composition of the skin mycobiota in healthy and pathological conditions have recorded shifts at the fungal species level in association with various disease conditions. Future studies should focus on the intra-species diversity of relevant skin fungi, given the large variations that

exist in some species and the impact that such variations can have on fungal pathogenicity, as it was recently shown for *C. albicans* isolates from inflammatory bowel disease patients.¹¹¹ Knowledge about the functional relevance of dysbiosis of the skin mycobiome in (immuno) pathology is sparse and future efforts should be directed towards mechanistically dissecting the consequences of genus, species and strain level variations for fungus-fungus, fungus-bacteria, and fungus-host interactions and the outcome of such interactions on health and disease. This should include multi-omics studies investigating the fungal proteome, secretome and metabolome as well as genetic approaches. Full understanding of how skin fungi modulate health and disease unavoidably involves dissecting the antifungal immune mechanisms at a cellular and molecular level in humans, animals and experimental model system. When studying naturally colonized hosts, the analysis of the immune response should not be limited to the blood, which is most readily accessible, but focus on the skin itself. Likewise, experimental systems should be chosen conscientiously to assure that the chosen models accurately mimic relevant parameters of the human/animal skin. Recently introduced models offer promising opportunities.^{56,112,113} Dissecting the interaction network of immune and non-immune cells in the skin during commensalism, fungal infection, and fungal-associated diseases will advance the understanding of the role of antifungal responses in homeostasis and disease. When studying adaptive antifungal immunity, antigen-specific approaches are advised to clarify the contribution of antifungal T cells in skin pathologies, such as the role of *Malassezia* allergen-specific T cells in the pathogenesis of AD. T cell receptor sequencing, determination of cross-reactivity, and expression of key effector genes at a single cell level will help to gain the necessary resolution in experimental models and in patients for understanding the emergence of pathogenic T cells in an otherwise protective context. Integrating a neuroimmunological perspective may further help elucidating the link between initiation of antifungal immunity and chronic skin conditions characterized by itching and other neurological manifestations such as AD and psoriasis. Together, this will shed light on the microbial and host determinants mediating immunosurveillance during homeostasis and driving pathogenesis in clinically relevant skin diseases. These approaches will open new avenues for novel preventive, diagnostic, and therapeutic options benefiting the patients, given the recurrent, chronic, and life quality restricting nature of many of the concerned disorders associated with skin fungi.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the writing of this review article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORCID

Fiorella Ruchti  <https://orcid.org/0000-0002-4993-1127>

Salomé LeibundGut-Landmann  <https://orcid.org/0000-0002-5724-4837>

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