

# Alteration in skin mycobiome due to atopic dermatitis and seborrheic dermatitis

Cite as: *Biophysics Rev.* **4**, 011309 (2023); doi: [10.1063/5.0136543](https://doi.org/10.1063/5.0136543)

Submitted: 27 November 2022 · Accepted: 22 February 2023 ·

Published Online: 13 March 2023



View Online



Export Citation



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## ABSTRACT

A microbiome consists of viruses, bacteria, archaea, fungi, and other microeukaryotes. It influences host immune systems and contributes to the development of various diseases, such as obesity, diabetes, asthma, and skin diseases, including atopic dermatitis and seborrheic dermatitis. The skin is the largest organ in the human body and has various microorganisms on its surface. Several studies on skin microbiomes have illustrated the effects of their composition, metabolites, and interactions with host cells on diseases. However, most studies have focused on the bacterial microbiome rather than the fungal microbiome, namely, mycobiome, although emerging evidence indicates that fungi also play a critical role in skin microbiomes through interactions with the host cells. I briefly summarize the current progress in the analysis of mycobiomes on human skin. I focused on alteration of the skin mycobiome caused by atopic and seborrheic dermatitis, with an emphasis on the *Malassezia* genus, which are the most dominant fungi residing here.

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## INTRODUCTION

Most multicellular eukaryotes are closely associated with microorganisms that they host and are together considered metaorganisms (Berg *et al.*, 2020). A microbial community in the human body is termed microbiome and is composed of viruses, bacteria, archaea, fungi, and other microeukaryotes. Microbiomes in living organisms are considered an inseparable part of the hosts and play functional roles that affect their health (Berg *et al.*, 2020). Disruption of the diversity of a microbiome in the human body due to intrinsic or extrinsic factors is called dysbiosis. It influences host immune systems and causes various diseases, such as obesity, diabetes, and asthma (Hooks and O'Malley, 2017; Bello *et al.*, 2018, Upadhyay *et al.*, 2022; and Zubeldia-Varela *et al.*, 2022). Therefore, the microbiome compositions in different organs, such as the respiratory tract, uterus, vagina, and digestive tract, have recently been analyzed extensively.

The skin is the largest organ in the human body, and various microorganisms are present on its surface. However, the composition

of microbiomes differs in different skin regions because of variations in anatomical and chemical factors, such as temperature, humidity, and sebum content (Oh *et al.*, 2014; Cundell, 2018). Several studies regarding skin microbiomes have highlighted the effect of their composition, metabolites, and interactions with host cells on human skin diseases, such as atopic dermatitis (AD) and seborrheic dermatitis (SD). However, most studies were concentrated on bacterial communities on the skin although other microorganisms, including fungi, play a critical role in the interactions between the skin microbiome and host cells. A metagenome analysis revealed that fungi, mainly *Malassezia restricta* and *M. globosa*, constituted 3.9%–5.0% of the microbiomes in most skin sites, while the external auditory canal, retroauricular crease, and glabella, had 16.86%–5.1%, 7.56%–4.2%, and 7.16%–4.0% fungi in the skin microbial communities, respectively (Oh *et al.*, 2014). Moreover, dysbiosis of the fungal microbiome, termed mycobiome hereafter, can cause many skin diseases, including AD and SD (Paulino, 2017; Schoch *et al.*, 2019; and Szczepanska *et al.*, 2022).

The importance of skin mycobiome in skin homeostasis and disease development is just emerging; therefore, only a limited number of studies regarding the structure of fungal communities on the human skin and their influence on diseases or the impact diseases have on them is available. We briefly summarize the current progress in the analysis of mycobiome of the human skin, with a focus on *Malassezia*

fungi and their role in the alteration of skin mycobiome due to AD and SD when compared with that of healthy controls.

### MYCOBIOME IN ATOPIC DERMATITIS

AD is a chronic and often relapsing inflammatory skin disease characterized by eczematous lesions, pruritus, and skin dryness. AD is common worldwide with a prevalence of 10%–20% and 3%–5% in children and the general population, respectively (Williams *et al.*, 2008; Ring *et al.*, 2019; and Fasseeh *et al.*, 2022). The pathophysiology of the disease is complicating and caused by multifactorial factors, including an abnormality in the epidermal barrier function that could be genetic or acquired and an immunologic disorder due to abnormal immune responses to antigens that often occur with increased T helper 2 (Th2) cells, which express interleukin-4 (IL-4)/IL-13, Th22, and Th17 cytokine activations and increased serum immunoglobulin E (IgE) levels (Leung and Guttman-Yassky, 2014). AD is often characterized by disruption of the epidermal barrier function, which causes decreased hydration, altered lipid composition, abnormal lamellar organization, increased skin pH, and decreased diversity of skin microbiota accompanied by an increased abundance of *Staphylococcus aureus* (Weidinger and Novak, 2016). The null mutation in the filaggrin (*FLG*) gene encoding filaggrin (FLG) is reported to be significantly associated with epidermal barrier impairment in patients with AD. However, how filaggrin deficiency contributes to AD is still not fully understood (Moosbrugger-Martinez *et al.*, 2022). FLG deficiency is associated with altered diversity of skin microbiota, i.e., reduced abundance of proteolytic gram-positive anaerobic cocci (GPAC), such as *Finegoldia*, *Anaerococcus*, and *Peptoniphilus* genera, which utilize histidine-rich FLG as a nutrient (Zeeuwen *et al.*, 2017). Another study revealed reduced abundance of Proteobacteria, such as *Acinetobacter*, *Enhydrobacter*, and *Microvirgula*, along with an increased abundance of *Cutibacterium* and *Firmicutes*, *Staphylococcus* in particular. Moreover, skin microbiomes in FLG-deficient individuals demonstrated greater similarity to those of patients with AD than those of individuals with normal FLG did (Baurecht *et al.*, 2018). A previous study suggested that AD is strongly associated with dysbiosis of the skin microbiome, which is evident in the reduced richness and diversity of bacterial communities and increased abundance of *S. aureus* (Alam *et al.*, 2022). *S. aureus* produces virulence factors, such as phenol-soluble modulins and proteases, which disrupt the host's skin barrier (Hirasawa *et al.*, 2010; Nakagawa *et al.*, 2017). Moreover, increased abundance of *S. aureus* is often related to reduction in skin commensal *Staphylococcus* species, such as *S. epidermidis* and *S. hominis*, which selectively produce an antimicrobial peptide against *S. aureus* (Nakatsuji *et al.*, 2017).

Most research on skin microbiomes to study impaired skin barrier functions due to microbes is concentrated on bacteria. However, recent studies have demonstrated the critical role played by fungi in skin microbiomes. A shotgun metagenome analysis showed that fungal presence in healthy human skin was lower (0.36%–16.86%) than the bacterial one, with a predominance of *Malassezia* species, especially *M. restricta* and *M. globosa* (Oh *et al.*, 2014). *Malassezia* is a lipophilic yeast; hence, its chief residing site is skin affected by SD. A total of 18 *Malassezia* species have been reported, and the genomes of most of them have been sequenced. Their analysis revealed that the lipid dependency is

caused by the absence of the gene encoding fatty acid synthase (Xu *et al.*, 2007; Park *et al.*, 2017; and Cho *et al.*, 2022).

Several studies have suggested a strong association between *Malassezia* and AD. For example, sensitization rates against *Malassezia* were higher in patients with AD; moreover, they exhibited *Malassezia*-specific serum IgE antibodies (Kieffer *et al.*, 1990; Ring *et al.*, 1992). Furthermore, various immunogenic proteins secreted by *Malassezia* induced specific IgE responses (Glatz *et al.*, 2015).

Although accumulated evidence suggests a critical role of fungi in AD, studies to analyze mycobiomes using a culture-independent method in the lesional and nonlesional skin sites of patients with AD having different geological and ethnic backgrounds are limited. An early study using polymerase chain reaction (PCR) with specific primers for each *Malassezia* species in a Japanese cohort with AD showed that *M. globosa* and *M. restricta* were detected more frequently than other *Malassezia* species, such as *M. furfur* and *M. sympodialis*, in the lesional skin sites. Moreover, AD skin lesions demonstrated a higher diversity of *Malassezia* than healthy skin did (Sugita *et al.*, 2001). Similarly, while patients with mild and moderate head and neck AD exhibited a predominance of *M. restricta* over *M. globosa*, those with severe head and neck AD demonstrated an equal abundance of these species (Kaga *et al.*, 2011).

A whole metagenome analysis of the antecubital fossae of individuals in Singapore having a history of AD, designated as AD-susceptible individuals, was performed between flares, and the results were compared with those obtained from the analysis of healthy controls. Overall, fungal abundance was higher in skin affected by AD than in healthy controls, and *M. globosa* and *M. restricta* were predominant in all the investigated skin sites. Moreover, *M. dermatis* and *M. sympodialis* were predominant in skin affected by AD, while *M. globosa* was relatively more abundant in healthy controls. Thus, fungal diversity in skin mycobiome varies between AD-susceptible individuals and healthy controls (Chng *et al.*, 2016).

Amplicon sequencing analysis of multiple skin lesions in a cohort with AD in Denmark was performed using the 18S rRNA gene. *M. restricta* and *M. globosa* were most prevalent in all the tested skin sites, although a decreased abundance of *M. restricta* in skin affected by AD was observed. Moreover, an increased abundance of the microscopic mite *Demodex folliculorum* and the fungus *Geotrichum candidum* was found in skin affected by AD than in healthy skin (Edslev *et al.*, 2021). Similarly, another study in which amplicon sequencing analysis was performed using internal transcribed spacer region (ITS) primers in a Korean cohort with AD showed that the *Malassezia* species were the most detected fungi among fungal communities in both AD and healthy skin. *M. restricta* and *M. globosa* were most dominant; moreover, *M. sympodialis* were found in both groups (Han *et al.*, 2018). Furthermore, fungal community diversity was higher in skin affected by AD than in healthy skin. AD-specific *Malassezia* species, including *M. slooffiae*, *M. obtusa*, and *M. yamatoensis*, were identified (Han *et al.*, 2018). Additionally, a recent study involving a cohort with AD in Switzerland showed that *M. restricta* and *M. globosa* were the two most dominant fungi in the human skin, regardless of AD severity. However, the abundance of *Malassezia* was decreased in severe AD skin lesions than in mild and moderate AD skin lesions and healthy skin. In contrast, diversity of other fungal genera, including *Candida*, *Debaryomyces*, *Aureobasidium*, and *Penicillium* were high in severe AD skin lesions (Schmid *et al.*, 2022).

Scalp mycobiome in Korean patients with AD having scalp dermatitis was determined by amplicon sequencing analysis using the ITS region. *Malassezia* was the most predominant fungus, and fungal diversity was higher in AD skin lesions than in healthy controls. *M. restricta* was most abundant followed by *M. globosa* in both AD-affected and healthy skin samples. Furthermore, a significantly higher abundance of *Saccharomyces* and *Cladosporium* was observed in AD samples than in healthy controls (Woo *et al.*, 2022).

Although the number of the AD-associated mycobiome studies are limited, and cohorts from different geological and ethnical backgrounds were involved, several common features were noticed. First, regardless of the severity of AD symptoms, *Malassezia* is the dominant fungus found on the human skin, with *M. restricta* and *M. globosa* demonstrating the highest detection rates in both diseased and healthy skin. Second, in the AD skin lesions, fungal diversity is significantly increased while the abundance of *Malassezia* is decreased (Fig. 1). However, more systematic investigations are required since the reviewed studies had relatively small sample sizes and used different sampling and sequencing methods.

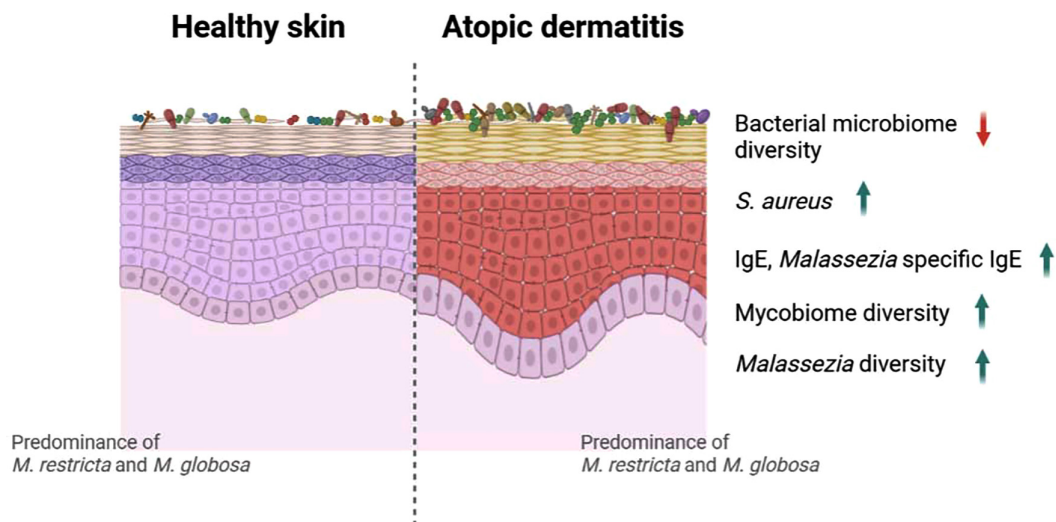
### SKIN MYCOBIOME IN SEBORRHEIC DERMATITIS

SD is a common chronic inflammatory skin disorder presenting in areas rich in sebaceous glands (scalp, back, face, and chest). Approximately 3% of the adult population experience SD, and a higher prevalence is reported in patients with immune deficiency and neurologic diseases, such as Parkinson's disease (Kim *et al.*, 2016), with more than 50% of patients with Parkinson's disease developing SD (Rietcheck *et al.*, 2021). Several underlying factors, including alteration of production and composition of sebum and disruption of epidermal barrier function, are considered to contribute to SD. Moreover, *Malassezia* is regarded as one of the main predisposing factors for SD because increased fungal counts are often observed while the disease

progresses, and antifungal treatment alleviates the symptoms (Wikramanayake *et al.*, 2019). Although the pathological role of *Malassezia* in SD is not yet fully understood, several of its characteristics likely contribute to the progress of SD. *Malassezia* fungi secrete multiple lipases that hydrolyze triglycerides in human sebum and produce unsaturated fatty acids, such as oleic acid, which may cause dandruff development resulting in flaking of skin lesions affected by SD (DeAngelis *et al.*, 2007; Park *et al.*, 2021). Moreover, the scalp and facial lesions in patients with SD exhibited hyphae formation by *Malassezia* cells, whose morphological characteristics may contribute to disease development (Li *et al.*, 2022).

Innate immune response against *Malassezia* may also be involved in SD. When the skin barrier function is impaired, *Malassezia* may be able to penetrate the epithelial tissue to interact with antigen-presenting cells, such as neutrophils, macrophages, and dendritic cells, and induce activation of the NLRP3 inflammasome leading to IL-1 $\beta$  secretion, which also contribute to the development and progress of SD (Kistowska *et al.*, 2014). A recent study suggested that *Malassezia* induces IL-17 cytokine production because Mpz13-knockout mice displayed SD-like phenotype, including increased IL-17 cytokine production (Wikramanayake *et al.*, 2017; Sparber *et al.*, 2019).

Dandruff is a type of SD that mainly affects the scalp, making it itchy and scaly but often without inflammation (Borda and Wikramanayake, 2015). The effect of mycobiome on SD was first investigated by comparing fungal and bacterial communities in dandruff-affected and healthy scalps. The analysis of dandruff samples from a cohort in France using fungal-specific PCR amplification, cloning, and sequencing methods revealed that the most abundant fungal species on scalps with and without dandruff was *M. restricta* (84% and 97%, respectively), and *M. globosa* and *M. sympodialis* accounted for less than 1% in both groups. Furthermore, *M. restricta* was more abundant in scalps affected by dandruff than in the healthy controls



**FIG. 1.** Graphical depiction of altered microbiome in skin affected by atopic dermatitis (AD). Several studies on bacterial microbiomes demonstrated reduced diversity of bacterial communities and increased abundance of *Staphylococcus aureus* in AD-affected skin than in healthy skin. In contrast, studies suggested increased diversity of mycobiomes, specifically that of *Malassezia* species. *Malassezia*-specific immunoglobulin (Ig) E increased, and high IgE levels were observed in patients with AD. Furthermore, most mycobiome studies commonly showed that *M. restricta* and *M. globosa* were predominant in both healthy and AD-affected skin. The image was prepared using Biorender.com.

(Clavaud, et al., 2013). Considering bacterial species, the population of *S. epidermidis* rose, while that of *Cutibacterium acnes* reduced in scalps affected by dandruff than in the healthy controls. Moreover, the *M. restricta*/*C. acnes* ratio was 0.37, which was significantly higher in scalps affected by dandruff than in healthy scalps, in which the ratio was 0.012 (Clavaud et al., 2013). ITS amplicon sequencing analysis to compare microbiome structures between individuals with dandruff and healthy controls in China showed that the most predominant fungi were *M. restricta* (88.5%) and *M. globosa* (5.1%). Moreover, compared with the fungal mycobiome, bacterial microbiome was more strongly associated with dandruff severity. While the abundance of *Cutibacterium* was significantly reduced, that of *Staphylococcus* was high in the same scalp samples with dandruff (Xu et al., 2016). The recent mycobiome analysis conducted via ITS amplicon sequencing in Korea showed that *M. restricta* and *M. globosa* were predominant on the scalp. The population of *M. restricta* was high and that of *M. globosa* was low in scalps affected by dandruff, suggesting a strong association between *M. restricta* and higher disease incidence. Moreover, dysbiosis of fungal communities may contribute to scalp SD development (Park et al., 2017). Similarly, another study in China indicated that *Malassezia* is one of the most predominant fungi on the scalp. Furthermore, the fungal diversity was higher in healthy scalps than in those affected by dandruff, with an increased abundance of *Malassezia* in the scalp affected by dandruff than in the healthy scalp. This observation was common to that in other studies although the tested samples differed geologically and ethnically (Lin et al., 2021).

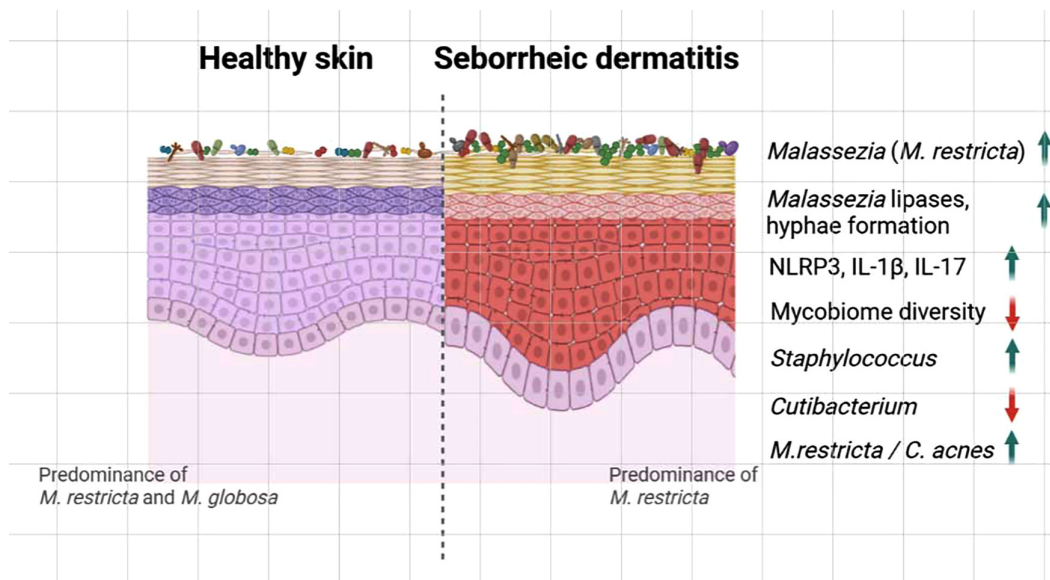
A novel *Malassezia* species, *M. arunalokei* has been recently reported (Honnar et al., 2016). A study conducted to compare the distribution of *M. arunalokei* between three skin sites (scalp, forehead, and cheeks) of patients with SD and healthy individuals showed that

the abundance of *M. arunalokei* was similar in the patient and healthy individual groups. However, the concentration of *M. arunalokei* was higher on the forehead and cheeks than on the scalp in both the groups, suggesting that the fungus is not associated with SD but rather with the skin site (Cho et al., 2022).

Apart from research to study abundance, a study to investigate the alteration of facial mycobiome in patients with SD after antifungal drug treatment was conducted (Tao et al., 2022). Topical ketoconazole, which is widely considered the most effective treatment for fungus-associated skin conditions, such as SD, had a clinical efficacy of 63%–90% (Choi et al., 2019). *Malassezia* is the most predominant fungal genus on both SD-affected and healthy facial skin. The basal structures of facial mycobiome in patients with facial SD were analyzed, and the abundance of *Malassezia* was significantly higher in the lesional skin sites than in the healthy controls. Moreover, fungal diversity was significantly lower with increased populations of *Candida* and *Aspergillus* in both lesional and nonlesional skin sites of patients with facial SD than in the healthy controls. Fungal diversity significantly increased after ketoconazole treatment when compared with the baseline (Tao et al., 2022). Monitoring of scalp mycobiome before and after ketoconazole treatment revealed increased fungal diversity and reduction of *Malassezia* on the scalp of patients with SD patients than in the healthy controls (Massiot et al., 2022). Overall, most culture-independent mycobiome analyses of scalp dandruff and facial SD suggest that the abundance of *Malassezia*, *M. restricta* in particular, increases and mycobiome diversity reduces with disease progression (Fig. 2).

## CONCLUSION

Evidence from previous research showed that AD and SD, which are the most common skin diseases, are closely associated with skin



**FIG. 2.** Graphical depiction of altered microbiome in skin affected by seborrheic dermatitis (SD). Studies demonstrated reduced diversity of fungal communities and increased abundance of *Malassezia restricta* in SD-affected skin than in healthy skin. Studies also suggested increased expression of lipases and hyphae formation in *Malassezia*. Activation of the NLRP3 inflammasome leading to IL-1 $\beta$  secretion and increased IL-17 cytokine production was also observed in the SD skin lesion. Furthermore, bacterial microbiome analysis demonstrated increased abundance of *Staphylococcus*, while *Cutibacterium* was reduced. The higher *M. restricta*/*C. acnes* ratio in scalps affected by SD compared to that in healthy scalps was also reported. The image was prepared using Biorender.com.

microbiomes, and the fungal constituents of microbial communities play a critical role in homeostasis, host interactions, and disease development. However, most culture-independent microbiome analyses of the human skin are focused on bacterial rather than fungal communities. Therefore, the effects of mycobiomes on human skin health and diseases are largely unknown.

The number of studies conducted to understand the role of mycobiome in the skin environment is limited; nevertheless, several remarkable findings have been revealed. While AD increased fungal diversity, SD decreased it, when compared with that on the healthy skin. Whether this is related to the different influences of the diseases or the differences in the fungal communities is not clear. Although the currently available data on skin mycobiomes are from persons of different geographical and ethnical backgrounds, almost all the studies suggested that *Malassezia* is the most predominant fungal genus in the skin mycobiota. Moreover, amplicon sequencing and metagenome analysis revealed that abundance of *Malassezia* is highly and positively correlated with development of AD and SD. However, our knowledge regarding *Malassezia* in the skin environment needs to be expanded. Uncertainties regarding the roles fungi play as essential members in skin microbiomes and the consequences of host–fungus interactions remains, and further research is required to clarify them.

## ACKNOWLEDGMENTS

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (Grant Nos. 2021M3A9I4021431 and 2022R1F1A1065306).

## AUTHOR DECLARATIONS

### Conflict of Interest

The authors have no conflicts to disclose.

### Author Contributions

**Won Hee Jung:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Resources (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead).

## DATA AVAILABILITY

All data are publicly available.

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