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The Importance of Investigating the Fungal Community (Mycobiome) in Dermatology R&D

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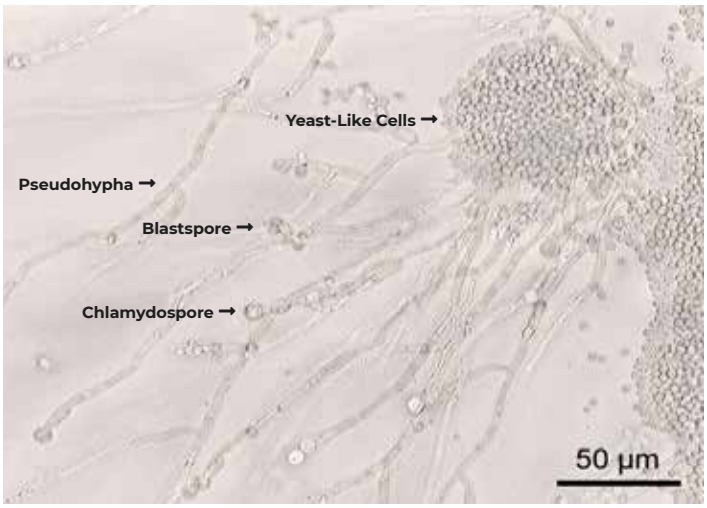
Introduction

Our skin microbiota contains both bacteria and fungi that serve important roles in the health of the dermis. Unfortunately, an imbalance in either can easily result in poor skin health and adverse skin conditions. The mycobiome (the fungal community) specifically is an integral part of our microbiota and plays a significant role in health and disease. This article highlights why the mycobiome should be considered when developing pharmaceutical and cosmetic products in order to maintain healthy skin and prevent skin disease.

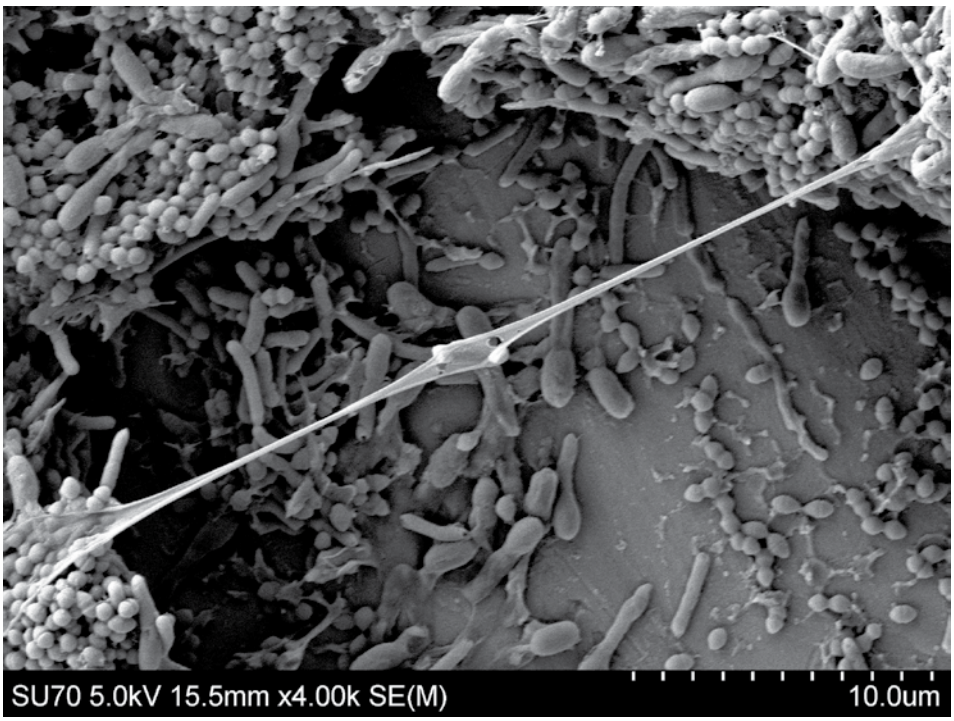
The mycobiome of human skin is very diverse and composed of many varieties of fungal species in both healthy individuals and those with skin disease. In fact, most of the fungal species found on the skin are commensal because they are not known to cause any harm or disease to the host.[1-3] Two of the most common fungal species that are found on human skin are *Malassezia* and *Candida*.[4] Fungi typically grow best on areas of skin that have a high presence of oil or fatty residues such as the top of the head and forehead, but are less abundant on other areas such as the back.[4] Outer dermis layers tend to have much less fungal diversity than the internal mucosal membranes and the feet due to the higher temperatures and humidity associated with these locations.[4] Unfortunately, changes to the number and diversity of fungi in the skin has been shown to lead to lowered skin immunity and adverse effects to the physiology of the dermis.[5]

Budding Malassezia spores (S). Image from: Ran Yuping et al

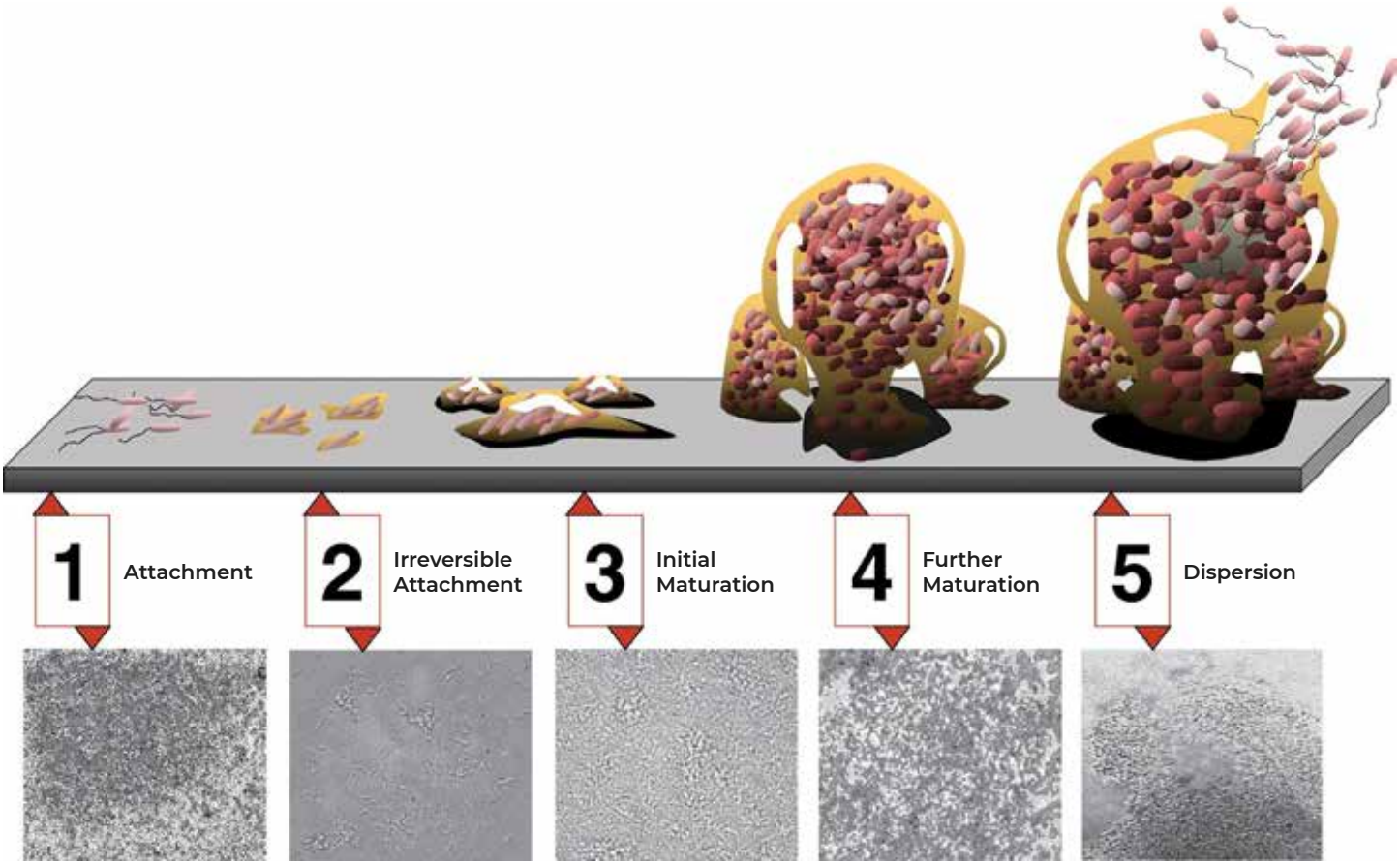


Candida albicans. Image from: Y tambe

The impact of an unsupportive microbiome on skin health is further compounded when fungal and bacterial communities work together for their own mutual benefit leading to adverse effects for the host.[6] For example, during wound healing, a multi-species population of various fungal and bacterial species was found to create complex biofilms that protect the species of the microbiome.[7] In this environment, fungal virulence factors increase while both fungal and bacterial species have a higher resistance to antimicrobial medications.[6] This ultimately leads to an unbalanced microbiome which can result in tissue damage. In fact, it was determined that the levels of fungal species were higher in chronic non-healing wounds when compared to normally healing wounds.[8] It is, therefore, important to consider the impact of bacteria, fungi, and the microbiome as a whole when examining skin health and disease prevention.



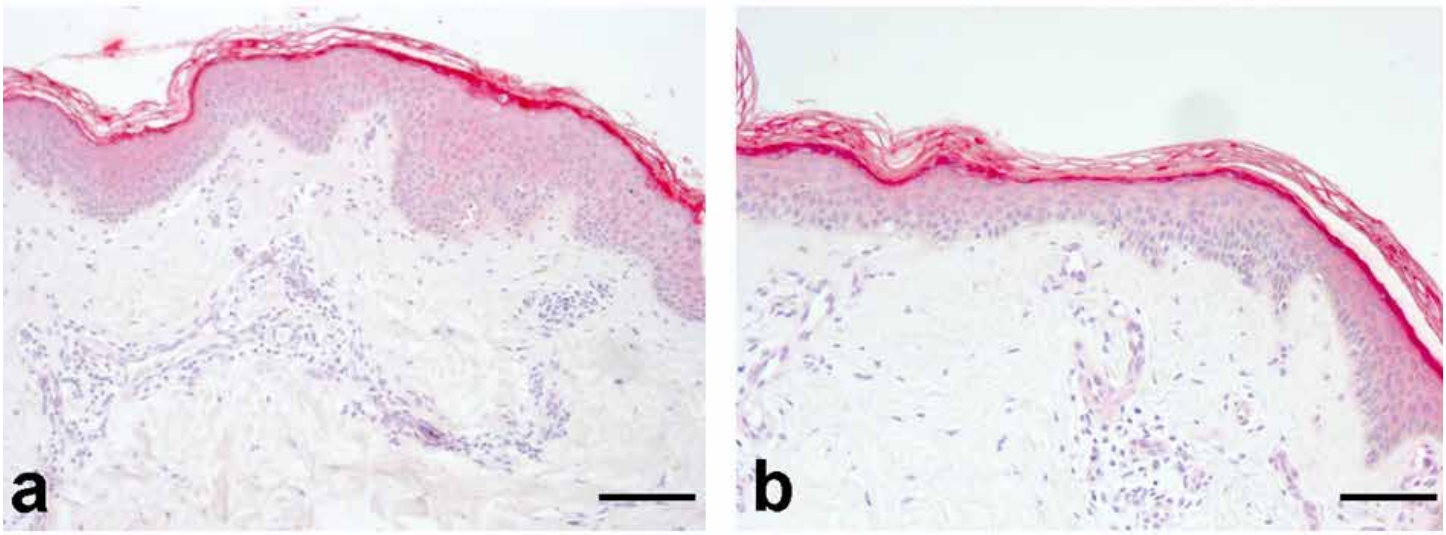
Mixed culture biofilm on a microscopic level. Image from Krzysztof A. Zacharski



The stages of biofilm development. 1) Attachment, 2) irreversible attachment, 3) Initial maturation, 4) Further maturation, 5) Dispersion. Image from: D. Davis

Disregarding the impact that consumer products may have on the microbiome can ultimately lead to an imbalance of fungal diversity that will negatively impact skin structure and could result in a number of diseases such as atopic dermatitis, psoriasis, acne vulgaris, rosacea and seborrheic dermatitis.[9] In addition, this imbalance will also affect the skin's healthy look, potentially reducing the benefits of cosmetic products. Characterizing the effects of particular products on the microbiome can provide valuable information about the potential positive or negative impacts that may occur in the skin after prolonged use of a particular product. Furthermore, development of pharmaceutical or cosmetic products should consist of a mindful attention to potential impacts to the mycobiome and the bacteriome in order to avoid adverse skin conditions and instead improve overall skin health.

SUPPORTING PILLAR 1: **ATOPIC DERMATITIS**



Skin biopsies stained with anti-FLG2 antibody. A) Atopic dermatitis skin lesion B) non-lesioned atopic dermatitis skin. Scale bars: 60 µm. Image from: Zhihong Wu,Britta Hansmann,Ulf Meyer-Hoffert,Regine Gläser, Jens-Michael Schröder

Atopic dermatitis is a skin disease that can be linked to the host's genetics as well as external environmental factors.[10] Atopic dermatitis is a form of eczema that is caused, in part, by an abnormal immune response and increased levels of inflammation in the skin. Symptoms include dry, itchy and cracked skin, which is found on the upper body, face, knees and elbows. Atopic dermatitis is a chronic condition that can persist throughout a person's lifetime. The regularity of compromised dermis layers in people with this disease often leads to frequent skin infections such as those linked to the presence of the bacteria *Staphylococcus aureus*.[11] Treatment typically consists of oral medications such as antihistamines and antibiotics as well as topical lotions including corticosteroids and immunomodulators.

Recent studies have shown that people with atopic dermatitis have an imbalance in both bacteria and fungi. Specifically, studies of the bacterial communities of the skin have shown that microbiome diversity is inversely correlated with disease severity in atopic dermatitis.[12] In fact, in a study involving children with chronic atopic dermatitis, bacterial diversity in the skin was positively correlated with disease severity and flare ups.[12] Even more interesting was the fact that this alteration to the microbiome was also correlated to the site of disease severity.[12] These findings suggested that there is a direct link to microbiome diversity and the presence and severity of atopic dermatitis. Furthermore, this study also noted that treatments for atopic dermatitis that resulted in a lower prevalence of disease flare ups also led to increased microbiome diversity.[12] The authors suggested multiple theories for this finding. One rationale was that treatments reducing the presence of *Staphylococcus aureus* may lead to an environment that is more conducive to bacterial diversity while a second theory postulated that atopic dermatitis treatments reduce all levels of bacteria simultaneously, allowing for a rapid and diverse repopulation.[12]

Sugita and colleagues were the first to study the diversity of fungal species in the context of atopic dermatitis by utilizing a genetic analysis approach called nested PCR, rather than relying on less efficient techniques involving fungal cultures.[13] The results of this study showed that there is an association between the fungus *Malassezia* and atopic dermatitis. Molecular-based analyses determined that the various species of *Malassezia* are more frequently detected and are more diverse in patients with atopic dermatitis than in healthy subjects.[13] Unlike the previously discussed study, these findings were not altered by the type of skin lesion tested. Even though *Malassezia* was found in both healthy and atopic dermatitis patients, the diversity of the microflora and production of antibodies in the skin varies greatly between healthy and diseased skin.

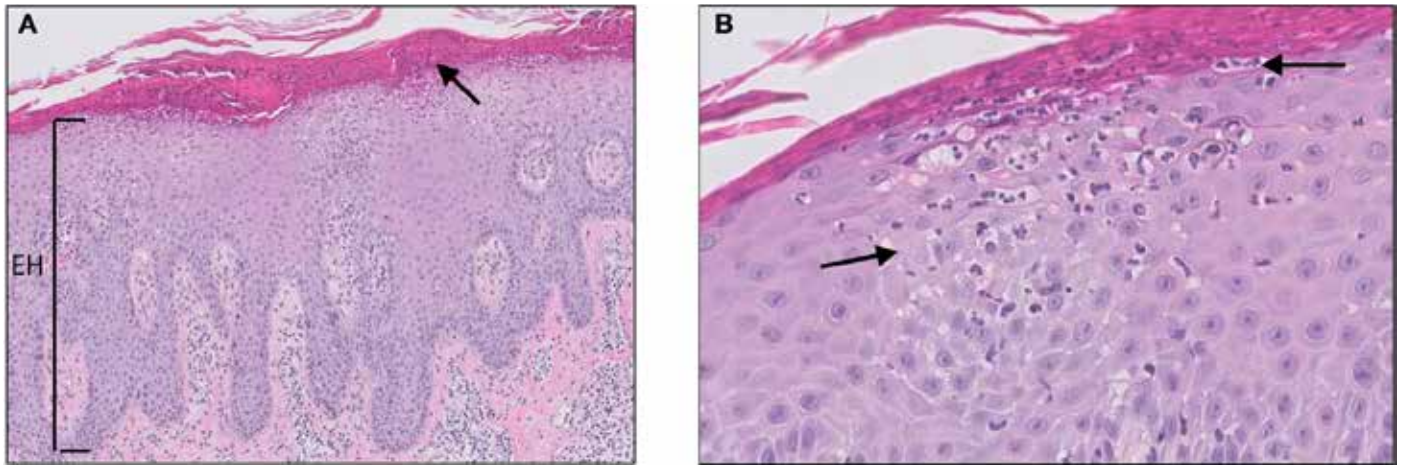
In attempting to determine the biochemical effects of the microbiome in patients with atopic dermatitis, numerous studies described the presence of IgE and reactive T cells that recognize Malassezia antigens in patients with active atopic dermatitis.[14–19] In 2003, Zargai and colleagues described seven *Malassezia* yeast species that created the production of IgE antibodies in atopic dermatitis patients.[14] Because mycobiome diversity is reduced in patients with atopic dermatitis, the authors acknowledged the importance of performing species specific allergen screenings in order to properly determine the prevalence of *Malassezia* in patients with active atopic dermatitis flare ups. In 2004, this group expanded on these findings and showed that samples from atopic dermatitis patients with IgE expression did in fact have specific interactions between the IgE antibodies and both heat shock protein (HSP) and manganese superoxide dismutase (MnSOD) antigens found in *Malassezia*.[15]

Atopic dermatitis on a patient (Source: Dr. Neil Korman)

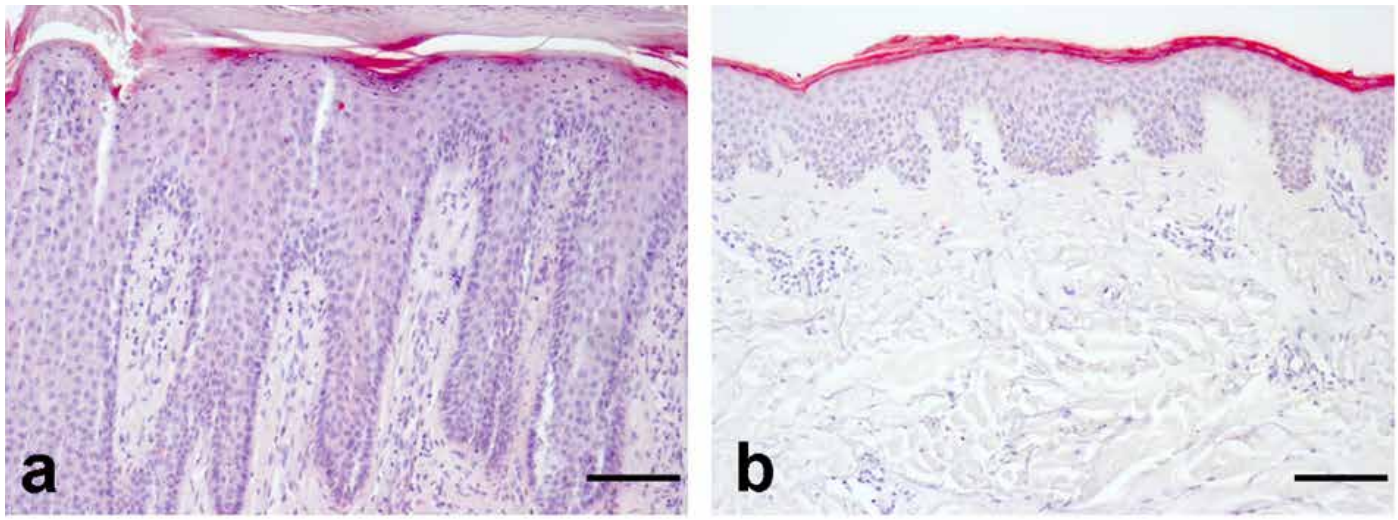
This IgE storyline continued with the findings from Balaji and colleagues in 2011 who established a connection between patient IgE expression and the high levels of T lymphocytes that are readily present in the skin of patients with atopic dermatitis.[16] This study was the first to determine that there is a T-cell mediated cross reactivity between thioredoxin found in humans with atopic dermatitis and a fungal protein found in *Malassezia*. Furthermore, it was noted that these T-cells also secrete the inflammatory proteins IL-17 and IL-22.[16,19] Such findings indicate that the increased presence of this yeast could be attributed to the immune dysfunction and increased inflammation that is characteristic of atopic dermatitis. Most recently, IgE-linked inflammation was determined to be the likely cause of atopic dermatitis in newborn children.[18] It was concluded that prenatal exposure to indoor mold is a likely environmental factor for the development of atopic dermatitis in these infants.

Overall, these studies highlight the importance of microbiome and mycobiome diversity in the prevention and reduction of atopic dermatitis disease flare ups. In fact, elimination of the infection-causing bacterial *Staphylococcus aureus* was not essential if overall skin microbiome diversity remained high.[12] Atopic dermatitis is a chronic recurring disease that has been directly linked to the fungal and bacterial diversity of the skin. Even though further investigation into the relationship between the mycobiome and atopic dermatitis is warranted, maintenance of a healthy and diverse skin fungal population appears to be an important factor in limiting the severity of this disease. Specific areas of further interest in the study of the impacts of the microbiome on atopic dermatitis include analysis of epigenetic and environmental factors on disease severity, big data meta analyses of diverse disease conditions on individual microbiomes, and the cause of alterations to the microbiome structure in regard to disease state.

SUPPORTING PILLAR 2: **PSORIASIS**



Micrograph of Psoriasis vulgaris. Jenny Giang, Marc A. J. Seelen, Martijn B. A. van Doorn, Robert Rissmann,Errol P. Prens and Jeffrey Damman



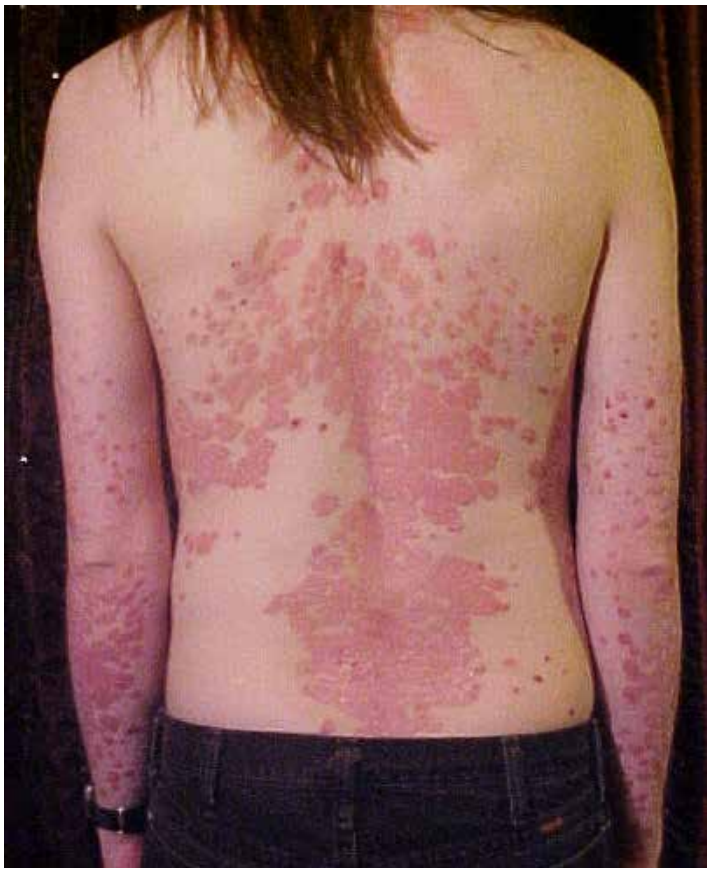
Micrograph of Psoriasis vulgaris. Jenny Giang, Marc A. J. Seelen, Martijn B. A. van Doorn, Robert Rissmann,Errol P. Prens and Jeffrey Damman

Psoriasis is an autoimmune disorder that is characterized by patchy, scaly and itchy skin. It is a fairly common disease that affects approximately 3% of the world population.[20] Similar to atopic dermatitis, psoriasis is a chronic disease that varies in its intensity and prevalence of flare ups from person to person. Unfortunately, 20% of patients also develop painful psoriatic arthritis.[21] Psoriasis is now described as a T cell-driven inflammatory disease that is specific to the dermis.[22]

Other than causes due to skin infection, psoriasis flare ups are also thought to be triggered by events such as stress, weather and skin injury.[20] Since psoriasis is an autoimmune disorder, immunosuppressants are often prescribed to reduce the immune system response to these triggers. Additionally, both light therapy and vitamin D analogues can be used to reduce the growth of skin cells in order to ultimately reduce the potential for skin scaling.

Studies have shown that individuals with psoriasis have both imbalanced and unstable bacterial and fungal communities.[23] A study conducted in patients with psoriatic skin lesions found that there is an increased relative abundance of the yeast *Malassezia* restricta on diseased skin as compared to healthy control skin.[24] This study also noted that the *Malassezia* present were more diverse in the psoriatic lesion samples rather than control samples.[24] In a separate study, it was also determined that decreased skin microbiome flora diversity is linked to an increased likelihood that a psoriasis patient will develop psoriatic arthritis.[21] This study, therefore, established that the microbiome is distinctly different between psoriatic patients and healthy controls.

In 2018, Pietrzak and colleagues reported that the detection rate of the fungal species *Candida* in samples



Psoriasis on back. James Heilman, MD

collected from the skin and mucosal membranes was significantly higher in psoriatic patients than those collected from the healthy controls.[22] This was particularly true of the samples collected from the oral mucosa milieux.[22] These results suggest that the autoimmunity disturbance in psoriasis may be one of the systemic diseases that predisposes one to oral *Candida* carriage and infection. In a second paper published in the same year, Lesan and colleagues determined that oral candidiasis is more prevalent in patients with psoriasis and is also related to disease severity.[25] It was not determined whether the presence of *Candida* leads to worsening psoriatic symptoms or vise versa, but the connection between psoriasis and these fungi is fairly certain.

Nevertheless, like many other microorganisms, *Candida* frequently colonize humans and are characterized as commensal organisms.[26] However, disruption of the balance of the normal microbiome can lead to an opportunistic infection due to immunodeficiency or a weakened mucocutaneous barrier.[27] It has been established that *Candida* plays an important role in triggering flares in psoriasis. In this regard, specific antigens of particular *Candida* species, especially *Candida* albicans surface proteins, have been shown to have superantigen-like effects that can result in the activation of T lymphocytes in a manner that is independent of antigen presentation and the excessive release of proinflammatory cytokines.[28,29]

The link between *Candida* colonization and alterations to the immune system remains an important consideration in the development of novel therapeutics targeted toward the microbiome or that contain side effects that impact the microbiome. In fact, a 2013 study published in the journal *Microbiome* determined that tissue undergoing active psoriatic disease likely promotes the recruitment of different types of fungi than normal tissue does.[30,31] This finding remains true when comparing diseased skin to healthy skin in the same individual.[31]

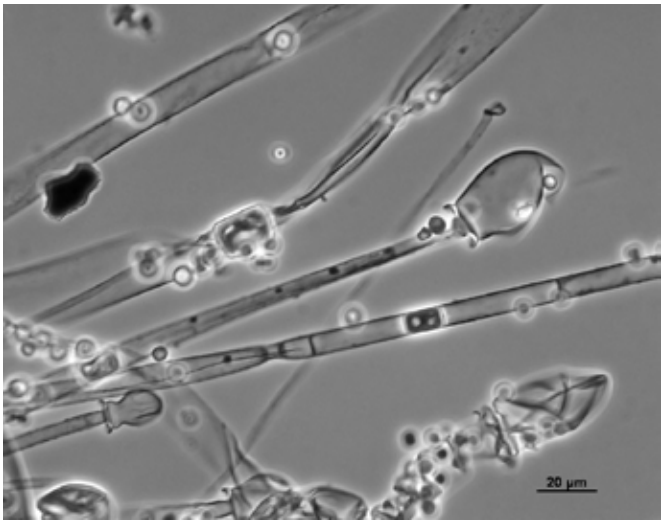
More recently, a 2020 paper highlighted the alterations to the skin mycobiome of psoriasis patients after treatment. Patients that were treated with inflammation inhibitors (namely TNFi or IL-17i) showed no significant changes to the skin mycobiome when compared to non-lesioned areas and lesioned areas in patients that did not receive treatment.[32] This lack of change to the mycobiome after treatment suggests that TNF and IL-17 inhibition does not impact the growth or lead to the destruction of common fungal species on the skin.[32]

Taken together, the findings from these studies suggest that determining the specific characteristics of healthy, disease associated, and post disease treatment mycobiome could prove to be extremely useful in the prevention of disease and the promotion of healthier skin. Future studies are required to determine advantageous methods of optimizing the presence and diversity of the beneficial species of the microbiome while eliminating species that are linked to disease pathways. Specifically, the findings described from these studies should be expanded to include a larger population and variety of subjects including various ages, geographic locations, genders, and disease location.

SUPPORTING PILLAR 3: **SKIN HEALTH AND APPEARANCE**

In addition to skin disorders and diseases, the skin microbiota is also implicated in several cosmetic skin problems such as impure skin, sensitive skin, dandruff, or body odor.[1] An imbalance of normal fungi and bacteria will negatively impact the skin structure, thus adversely affecting the cosmetic appearance of the skin. In a 12 week, double-blind, placebo-controlled study, Lee *et al*. examined the oral supplementation of the probiotic strain *L. plantarum* HY7714 in 110 middle-aged Korean subjects and found that there was improved cutaneous elasticity and increased skin hydration in volunteers of the experimental group.[33] The addition of the oral *Lactobacillus* supplement increased overall skin health leading to an anti-aging benefit that led to smoother looking skin by increasing the skin biodiversity.

In a study that examined the skin microbiome of healthy Japanese women, Shibagaki and colleagues found that there were striking alterations and diversities in the skin microbiome between healthy younger adults (ages 21–37) and older adults (ages 60–76).[34] Their findings suggest that the diversification of skin microbiome in adult women is primarily affected by chronological and physiological skin aging that is associated with the microbiota.[34] Specifically, they discovered that the microbial richness in the cheek and forehead microbiome, as well as the forearm and scalp, differed significantly between the two groups. Additionally, they showed that chronological age-related and unrelated skin clinical parameters correlate with the observed changes in skin microbiome diversity.[34]



Mucor racemosus sporangiophore. Image from: Medmyco

Unfortunately, diversity of certain microbiome species has also been linked to adverse skin conditions. In a 2020 study of Korean women, it was demonstrated that the mycobiome of people with sensitive skin was more diverse phylogenetically than those participants with non-sensitive skin.[35] Specifically, there was an increased presence of the bacteria *Lactobacillus* and the fungus *Mucor racemosus* but a decrease prevalence of the yeast *Malassezia restricta* on the dermis of sensitive skin participants.[35] These findings are very interesting and highlight the importance of developing cosmetics products based on the specific microbiome profiles of the product's intended users.

Ultimately, maintaining a healthy and diverse skin microbiome is essential to overall skin health. Beneficial microorganisms that live on human skin have been found to aid in many processes, including increasing antibacterial peptides, the formation of protective barriers or biofilms and even increasing the prevention of infection by harmful pathogens.[20] Further scientific study into the benefits of a stable and diverse microbiome are essential to the successful development of skin-based health and beauty products.

Conclusion

It has been stated that up to 1,000,000,000 (one billion) microorganisms can live in one square centimeter of human skin.[36] The mycobiome, or the fungal community, is an integral part of our microbiota and it plays a significant role in health and disease. Having a balanced mycobiome, as well as the bacteriome, will lead to the maintenance of healthy skin. It appears that fungi play a particularly important role in these processes by being a stabilizer for the health and strength of the ecological network and organization of the microbiome as a whole.[37] The healthy human microbiome has also been recognized as an immunomodulator in the prevention of many skin diseases.[38] However, an imbalance in the microbiome and mycobiome communities will impact the structure of the skin and result in a loss of elasticity, smoothness, and hydration. An imbalance could also lead to a number of skin diseases such as atopic dermatitis, psoriasis, acne vulgaris, rosacea, seborrheic dermatitis, and cause issues with wound healing.[1]

Characterization of the skin microbiome and mycobiome is complicated by the large variations that can be noted between individuals, cultures, ethnicities and demographic regions.[10,39] Interestingly, there is an age-related link to Malassezia colonization with fungal levels increasing from adolescence to adulthood.[4] Conversely, fungal diversity of Malassezia species decreases with age from childhood to adulthood.[4] It was hypothesized that the shifts in the microbiome during puberty are likely due to sebaceous gland increases in young adults.[40] Malassezia colonization is also more prevalent in men as compared to aged matched women.[4] Additionally, warm and tropical climates are associated with higher positive culture rates in individuals with healthy skin as well as significantly more diverse mycobiome on average.[41] These results provide further evidence of the unique and complicated nature of the human mycobiome in healthy individuals.

The findings based on the numerous studies summarized in this article clearly demonstrate that characterizing the mycobiome profile will provide insights into how we can rebalance and maintain a healthy microbiota. Increased interest, focus and understanding of the impacts of the human skin microbiome will lead to the discovery and development of novel therapies for the treatment and prevention of skin diseases and aid in the formation of consumer products that can effectively maintain skin health and wellness.

Topic	Symptoms	Chronic?	Bacterial Species	Fungal Species	Pathways
Atomic Dermatitis	dry, itchy, scraked skin	✓	*Staphylococcus aureus*	*Malassezia*	IgE expression
Psoriasis	patchy, scaly & itchy skin	✓ intermittent	Corynebacterium, Propionibacterium, Staphylococcus & Streptococcus	*Malassezia, Candida*	T cell-driven inflammatory disease
Health / Appearance	impure skin, sensitive skin, dandruff, body odor	✓	*Lactobacillus*	*Mucor racemosus, Malassezia restricta*	Many

About Dr. Mahmoud Ghannoum

Dr. Ghannoum is a professor at the Dermatology Department at Case Western Reserve University and University Hospitals Cleveland Medical Center. He has extensive hands-on experience investigating how the fungal and bacterial communities influence our skin in health and disease. He provides ready-to-use *in vitro* and *in vivo* models and access to clinical units to meet pharmaceutical, cosmeceutical, and biotech companies' R & D needs.

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