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The Role of the Scalp Microbiome in Health and Disease: *Malassezia*, Friend or Foe?

THOMAS L. DAWSON, JR
*A*Star Skin Research Laboratories, Skin Research Institute, Singapore, Singapore*
Department of Drug Discovery, Medical University of South Carolina, USA (T.L.D.)

Synopsis

The human microbiome has soared to scientific celebrity status, while the skin microbiome has been somewhat dragging behind. We now understand that microbiomes are central to humanity, with the human body consisting of more microbes than human cells and the microbes both being essential for maintenance of life and regulating diverse functions such as digestion, obesity, blood pressure, skin disease, and even brain function, mood, and personality. While the skin microbiome has lagged in investigation and understanding, we now know it influences many facets of skin health, including acne, seborrheic dermatitis (dandruff), psoriasis, atopic dermatitis, and rarer disorders, including pityriasis versicolor and folliculitis. Bacteria rule the gut microbiome, but fungi play an important role in skin, particularly the dominant eukaryote *Malassezia* yeast. *Malassezia* are present on all humans (and all warm-blooded animals), including healthy and diseased skin. The *Malassezia* clade consists of 18 species with numerous functionally distinct subspecies and strains, and it remains unclear how the functional differences are involved in skin health. Historically, *Malassezia* have been considered "commensal" organisms, defined as those who derive a benefit from their host (humans, as their food source) but have no impact, either positive or negative. A "mutualistic" relationship is one in which both partners benefit, and a "pathogenic" one in which one benefits and one is harmed. Hence, commensalism is the default situation where there is limited data. Now, with more evidence, it is becoming clear that *Malassezia* likely have all three roles in human skin.

INTRODUCTION

Why would a talk on skin microbiome be important in a hair care conference? In this case, it results from the internal divisions of consumer care companies, with vertical sections based on product form. As dandruff is most commonly treated with shampoos, dandruff is a hair care issue, despite it being a disorder and treatment paradigm relating to the skin microbiome. It is obvious why we have skin—it keeps bad things out and necessary things, like water, in. Skin is our "space suit" protecting us from a hostile environment. But the skin is also completely different from a space suit, as it is a living entity replenished every 14 to 21 days and covered in a microbial "skin" of its own. As skin is complicated and this audience is focused on hair, skin warrants a bit of introduction.

Address all correspondence to Thomas Dawson, thomas_dawson@asrl.a-star.edu.sg

SKIN BIOLOGY

Skin is a multilayered covering consisting of a "permanent" nonrenewing dermis covered by a continually renewing epidermis. The dermal layer is 2–3 mm thick, the epidermal layer 0.1–0.2 mm thick, and the overlying stratum corneum 10–20 μm. As the dermis is a nonrenewable layer, it ages along with our body and is primarily responsible for aging issues such as wrinkles and sagging. At the dermal or epidermal junction are stem cells that divide and differentiate into the tough outer stratum corneum, the sort of plastic wrap that covers our body. The entire epidermis will renew itself about every two months, but the stratum corneum should renew itself every 14 days. In "hyper proliferative" skin disorders such as dandruff, instead of renewing every 14 days, the stratum corneum will renew itself in only six or seven days (1).

It is generally accepted that the microbiology on skin resides in the stratum corneum (2,3). However, skin consists of many different environmental niches. Forearm skin is dry, it does not have sebum, and it can be considered desert wasteland and challenging environment for microorganisms. But when we consider the scalp, we have heavy sebaceous secretions and hair occluding and holding in water. Thus, on the scalp, there is an optimal environment for microbiology (4,5).

Another important consideration is we think of skin as a singular organ. If one were to remove the skin and spread it out, it would be about 2 m^2, and, for many years, that is how it was considered. But if one considers the topography, follicular openings, invaginations, and ridges, the surface area is closer to 25 m^2, on par with the gut and lung as a surface area for host–microbe communication (6).

SKIN MICROBIOLOGY

First, a few terms should be defined. A "microbiome" refers to the collection of microbial genomes present in a system. Hence, the "microbiome" does not do anything; it is a means of identifying what organisms are present. The "microbial community" is the collection of organisms, living and dead, that functionally interact with the host environment, and each other.

What is the microbiology living on or skin? There are on the order of 1–10 million microorganisms per cm^2. One reason skin microbiology is considered an easier research is because it is easier to sample. You can use a swab, tape strip, cup scrub, or even a q-tip and sample right off the skin's microbiome. It is also complicated by the specific environment, immune system, and sex, and many sites are completely structurally different. As one reads and learns about the skin microbiome, it is imperative to understand where people are sampling, what they are looking at, and how they are looking at it (3,7).

After sampling, the primary method for microbiome analysis is nonculture-based next-generation DNA sequencing, usually by one of two methods: amplicon or metagenomic. In amplicon sequencing, DNA is isolated from the sample and amplified via PCR to isolate unique microbial genomic regions. The resulting sequences are compared to existing databases to identify and count the different genomes. The primary insufficiencies with amplicon sequencing are that there may be microbes that are not amplified, as they are too different, fall out of consideration because of amplification bias, or do not exist in the

database. In shotgun metagenomics, the entire DNA sample is putatively sequenced without amplification. The main issues with shotgun metagenomics are the lack of organisms in the current databases and the lack of any quantitative nature. The amplicon databases, referred to as 16S for bacteria and ITS (intergenic transcribed spacer region) for fungi, are much more comprehensive than full metagenomic databases, particularly for eukaryotic organisms. Keep in mind that microorganisms are being discovered at a phenomenal rate, with many still unknown. When sequences are not found in the databases, they are clustered into "dark matter" and disregarded. Hence, there is often more uncharacterized dark matter in metagenomics than in amplicon sequencing. Finally, in shotgun metagenomics, the output is diversity, the relative abundance of population members. This does not provide any information on quantity of microbes, which remains an important part of microbiology. Using both techniques, one finds that the human skin microbiome generally consists of 93–97% bacterial genomes and 3–7% fungal genomes, and this very much depends on the body site (with fungi populating the oily sebaceous areas, including scalp, face, and back). The vast majority of the fungal community are *Malassezia*, with a more diverse bacterial community dominated by *Cutibacterium acnes* various *Staphylococci* (4,8).

FUNGI AND *MALASSEZIA*

Fungi is a vast kingdom. There are many different types, including mushrooms, mold, smut, and rusts. A famous toxic mold is *Stachybotrys chartarum*, a very dangerous mold to have in one's basement. Smuts and rusts are major agricultural pests, causing billions of dollars per year in damage to crops such as rice, corn, and citrus. *Malassezia* are yeasts, and, importantly, closely related to many plant pathogens. There are 18 known *Malassezia* species and dozens of functionally diverse strains (9).

This article now returns to the topic of nonculture-based microbiome detection methods: amplicon and metagenomics sequencing. With either method, the percent of the microbiome defined above is based as the number of genomes, implying there are 10 to 100 times more bacterial cells per skin unit area than fungal cells (8,10). An important difference is that fungi are gigantic compared to bacteria. The volume of a sphere varies with the cube of the radius and the volume of the cylinder with the square of the radius. So, when something is a few microns larger in diameter, it is tremendously larger in volume or biomass. *Malassezia globosa* or *Malassezia furfur* is conservatively a thousand times larger than bacteria (11). If there are 100 times more bacterial cells, then there are almost certainly at least as much interactive biomass from fungi. The biomass interacts with us, not the genome.

Another thing about mycology is that few people study it. Less than 10% of the microbiome publications consider fungi, and when one adds in skin, you get less than 1% of microbiome publications relating to skin fungi. In fact, fungi are so poorly investigated that in 2017, some students in California went to the grocery store and bought a packet of porcini mushrooms and sequenced their genomes. They identified seven previously undescribed species in a porcini packet on a grocery store shelf. Finally, mycology has been catching up in importance in large part because of public awareness and interaction, including since it became apparent that the Earth is a lot more like the Middle Earth in J.R.R. Tolkien's world because plants actually talk to each other through an underground fungal mycelium.

DANDRUFF

Now that we understand *Malassezia* and fungi, this paper will now discuss dandruff. Dandruff is big business—making the skincare industry a lot of money. The market associated with skin microbiology is estimated at more than $20 billion USD per year, with $5 billion of that being anti-dandruff shampoo alone. This makes dandruff a significant problem that accounts for a large percentage of dermatologist visits and a health care burden. As so many research publications focus on the gut and bacteria, skin eukaryotes are poorly understood. This is an exploitable knowledge gap and, hopefully, we can learn to exploit skin mycology to drive business and improve human health.

Dandruff represents a less severe version of seborrheic dermatitis, but both are the result of a similar aetiology (12). Dandruff consists of scalp flaking and pruritis (itch). Seborrheic dermatitis also includes visible irritation and may extend beyond the scalp to the eyebrows, nasal labial fold, and beard. But dandruff is more than flaking and itch. The stratum corneum is completely disrupted, mixed up, and disorganized and completely unable to perform its function, which is to protect us from what is outside and to keep our water in (13).

To understand what causes dandruff, it is useful to initially review historic treatment paradigms. Historically, the most effective materials used to treat dandruff had one commonality: antifungal efficacy. This may lead us to hypothesize that fungi are involved in dandruff genesis. As the scalp microbiome is dominated by *Malassezia*, it would also make sense that *Malassezia* that might be important in causing dandruff. The problem here is that *Malassezia* are found on a healthy scalp as well as one with dandruff. Many hours and dollars have been sacrificed investigating the cause of dandruff to enable better treatment design. Initially, when it was discovered in 1994 that *Malassezia* consisted of multiple species, we were convinced we would be able to identify a causative species and thereby target the right *Malassezia* (14). We executed a parallel group clinical study and compared dandruff sufferers with an inherent scalp flaking score (ASFS) of greater than 24 to normal subjects with an inherent scalp flaking score of less than 10. Unfortunately, the two groups were the same, and everyone had the same scalp microbiome (15). If this is correct, and it remains so even today, how can *Malassezia* be the cause of dandruff?

MALASSEZIA AND THEIR ROLE ON SKIN

COMMENSALISM

There are multiple types of microbe–host relationship terms: commensalism, in which one partner benefits but the other is unaffected; pathogenicity, in which one benefits and the other is harmed; and mutualism, in which both benefit (16). It has been long known that *Malassezia* inhabit the skin of all humans, with both healthy and diseased skin. In the absence of any other data, the default interpretation would be that *Malassezia* benefit from living on us, utilizing us as a food source and biological niche with no obvious benefit or harm, leading to definition of the relationship as commensal. Indeed, virtually all the technical literature prior to 2000 would classify *Malassezia* as commensals on human skin, perhaps occasionally being referred to an "opportunistic pathogen." Very likely, in some instances, this is a correct assumption. In other cases, we now think it likely that a more complicated relationship exists.

PATHOGENICITY

It is important to dig deeper and understand that *Malassezia* live on sebum, eating the oils on skin (17). Human sebum is created as sebaceous triglycerides that are secreted from the sebaceous gland. When there are few *Malassezia*, the skin is covered with mostly triglycerides similar to olive oil, which is good for your skin. When *Malassezia* are present, they break down the triglycerides that are good for your skin, and they are replaced by irritating free fatty acids. We hypothesized if *Malassezia* cause dandruff, these fatty acids might reconstitute dandruff. To test this hypothesis, we identified two groups of subjects for a clinical trial, one of dandruff sufferers (ASFS >24) and one of non-dandruff sufferers (ASFS < 8). We then removed the *Malassezia* with antifungal treatment and reduced all the flaking scores to <8 and performed a placebo controlled split scalp application of either oleic acid (the most abundant free fatty acid released from sebum) or its vehicle. The subjects who initially had dandruff begin flaking again at the treatment sites, and those flakes look exactly like human dandruff flakes. This indicates that application of a *Malassezia* metabolite, oleic acid, is able to induce a dandruff-like desquamation. Interestingly enough, in the subjects who did not initially have dandruff, the non-dandruff population, this no longer works. This divides human race into two groups—those who get dandruff and those who do not (15,17). For now, the individual susceptibility remains unknown. It may be a skin barrier problem in which the fatty acids are able penetrate better. It may be a host response to either the fatty acids or to a *Malassezia* metabolite that has penetrated through the skin. In any event, it is now clear humans can be divided into those who can get dandruff and those who do not. This is termed individual susceptibility and is common in microbially-mediated disease.

The concept of individual susceptibility in microbially-mediated disease also complicates how we design, execute, and interpret clinical trials and disease models. If one compares "diseased" to "normal" subjects seeking a causal microbe, if the disorder is based on an underlying individual susceptibility, it will be impossible to find the microbe. It will be present on both groups, unable to cause disease in the nonsusceptible group. Furthermore, the microbe and its entire pathogenic mechanism may be on the nonsusceptible group, simply unable to cause disease. This indicates we need to seriously consider the implications of clinical investigation into microbially-mediated disease. To elucidate the organism and mechanism, it would be essential to work with diseased individuals in which one can treat the disorder and observe changes in the microbiology and homeostatic mechanisms during treatment and reversion (3,11).

This also complicates understanding if a microbe is a pathogen, a commensal, or a mutual. Commensalism means that only one of the organisms benefit; in this case, *Malassezia* eat the sebum and digest us with no other effect. All this goes back to Heinrich Koch, a legend of microbiology because of his "postulates of disease" (18). In order for a microbe to cause a disease, it must be found on diseased, rather than healthy, organisms. You must be able to isolate the microbe, grow it up in pure culture, put it back on the healthy organism and cause the disease, and then reisolate it and show it caused the disease. These postulates worked great in the 19th and early 20th centuries, initiated germ theory, and brought about the modern era of medical research.

However, the world has now become more complicated (19). Koch's postulate that organisms must be found on all organisms with the disease, but not healthy organisms, stumbles on the concept of individual susceptibility. Even Koch himself in the early 19th

century knew there were asymptomatic carriers of tuberculosis, and now, we know that likely more than 90% of microorganisms are unculturable. Today, it is not easy to put disease causing microorganisms back on healthy people, making it more complicated. We need to understand that in all cases Koch's postulates do not always have to be fulfilled (16).

Let us return to this concept of pathogenesis and *Malassezia*. How can *Malassezia* cause dandruff if they are on everyone? If we consider susceptible individuals, people who have the possibility of getting dandruff for whatever reason:

- If you remove the fungi, the dandruff goes away.
- If you remove the bacteria, it does not.
- If you remove both the bacteria and the fungi, the dandruff gets better but at the same magnitude as if you removed only the fungi.
- If you create a resistant *Malassezia* and put it back on the same subjects that are under antifungal treatment, that dandruff returns.

These were experiments conducted and published in the 1960s and 70s and are high-quality studies (20–22). Additionally, in the experiment in which an isolated toxic metabolite is added back, even in the absence of *Malassezia*, dandruff returns (15). This makes a pretty strong case that *Malassezia* can be a pathogen, and we can prove that in susceptible individuals. If one looks exclusively at subjects who are susceptible to dandruff, the pathogenic mechanism can be described: *Malassezia* is on skin. They eat break down sebaceous lipids by secreting a lipase that breaks down the triglycerides. They consume a subset of saturated fatty acids, actually eating what is good for our skin. They then can proliferate; this is a commensal cycle. But that is not how it works. Unfortunately, *Malassezia* are unable to consume unsaturated fatty acids, and they are left behind on the scalp. They penetrate and break down the scalp's barrier, inducing a repair response, proliferation, and flaking (13).

MUTUALISM (PROTECTION)

Mutualism is a relationship in which both parties benefit. A recent example in the human–*Malassezia* relationship is in atopic dermatitis, a hyperproliferative skin condition characterized by redness, scales, and itching, usually on the appendages or trunk. In a longitudinal study comparing unaffected control individuals, affected AD lesions, and nonlesional sites in affected individuals, *Malassezia* were compared with shotgun metagenomics. The *Malassezia* as a group showed little difference. Even with *Malassezia restricta*, the species most commonly identified on skin, there is no real difference. However, upon examination of *Malassezia globosa*, the species that is the primary player in dandruff, it was found that there is not that much *M. globosa* in the lesions, and *M. dermatis* and *M. sympodialis* are measurably (but not significantly) higher. In this instance, it was apparent that different *Malassezia* species have very different activities (23). The hypothesized *M. globosa* protective mechanism AD involves secretion of an aspartyl protease, MGSAP1. Proteases are designed to break down proteins, and fungi usually employ them to prepare proteins for digestion. So, being a carnivore, *Malassezia* secretes a battery of proteases to eat our skin. However, it has now been demonstrated *in vitro* that secreted MFSAP1 is able to break down *Staphylococcus aureus* biofilms. *S. aureus* biofilm creation is closely linked to atopic dermatitis. While it is still open as to whether *S. aureus* biofilms *cause* atopic dermatitis, they are likely involved, and people with AD lesions have a significantly increased *S. aureus*

numbers and *S. aureus* biofilms, which are very hard to break down with treatment. So, *Malassezia* may be secreting an enzyme making life more difficult for *S aureus* (24). This sounds like a mutualist benefit, with *Malassezia*, in some cases, being beneficial for skin.

MOVING FORWARD

Now what? *Malassezia* represent many different species, some awaiting cultivation and others even awaiting identification. They do different things: they can do nothing, they can be good, or they can be bad. How do we move forward to understand and to treat dandruff and other common skin diseases impacted by *Malassezia*? How will we replace the broad-spectrum antifungal materials in shampoos? How are we going to design treatments that work?

Heinrich Koch's vision of microbiology remains the dogma, starting with parallel group studies comparing affected and unaffected populations, identifying microorganisms on affected subjects, culturing microbes from the infected individuals and putting them back into unaffected individuals to induce lesions, and then reisolating those microorganisms to confirm the correct affliction. Then, the investigator would design molecular entities to interrupt this cycle. I remain skeptical that this paradigm will be effective in most cases, and it has previously and repetitively been shown so. I think we need newer, more creative ways to be able to understand how the microbiota works.

The dogma is that there are fungi and bacteria on the skin. They secrete stuff and that affects the host. If one removes that microorganism, the impact on the host is also removed. Unfortunately, it is more complicated than that. Microbes talk to us, and they talk to each other. "Health" is when there is a healthy homeostasis in which the bacteria, fungi, and even viruses are in balance with the host (3). It is also become increasingly clear in that in fungal-mediated disease, the damage may not come from the fungi but from the host—where we have made an aberrant reaction to an otherwise benign organism and damaged ourselves (25). A clear example is COVID-19. The people who are sickest with COVID are not necessarily sick because of the virus. They are sick because their immune system has overreacted and attacked their lungs.

Instead of simplistic models in which we identify a fungus or bacteria and remove it from the system and everything will get better, we need to figure out what these communication molecules, "soluble modulatory factors," are. We know the host secretes antimicrobial peptides that affect bacterial and fungal populations, fungi reduce the skin pH, which is difficult for some bacteria, and fungi secrete antibacterial compounds and short chain fatty acids. Now, a number of labs are working on these soluble factors, in which microbes secrete materials that cause inflammation, block immune responses, and may even be anti-inflammatory. Only by tackling microbe–host interactions as a larger homeostasis are we going to get away from broad-spectrum antimicrobial materials.

In summary, we see the tip of an iceberg. We understand that skin is more complicated than we thought. We understand skin microbiology is complicated, and it is not just direct 1:1 pathogenesis or secretion. The microbes and host communicate with each other. To understand microbiology, one has to pay attention to the details and think about what the sample is, how to analyze that sample, and, very importantly, the clinical design. The human skin microbiome is important and involved in human health. Ignoring the microbiome in skin treatment design will not get the right answer. *Malassezia* are the

primary eukaryotes on skin and have many faces. They can be a commensal, a pathogen, or a mutualist. We need to first understand healthy homeostasis and what healthy skin actually is before we can progress. We need to understand how we are going to intervene and that classic intervention technologies may frequently fail. We must be more creative and clearer about how we investigate skin health if we will figure out the holistic system and understand what is actually going on in human skin health and disease.

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