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Host–microbe interactions: *Malassezia* and human skin

Elizabeth A Grice[1] and Thomas L Dawson 23*Jr[2,3]

The skin is our first line of defense, protecting us from invasion and evaporation. Its variable structure, changing geography, and complex immune repertoire provide a vast interface for our cutaneous microbial community. Skin is inhabited by many thousands of microbes, but this review focuses on the dominant eukaryote, *Malassezia*, and its host interaction. *Malassezia* compromises 17 species with variable niche specificities and differing pathogenic potential. It has been known as a skin inhabitant for over 100 years, and is now accepted to be on all warm-blooded animals. *Malassezia* occupy healthy and diseased skin, so their role as commensal or pathogenic organisms is complex. *Malassezia* interact with their host indirectly through immune interplay and directly via chemical mediators. While some interactions are known, many remain to be fully understood.

Addresses
[1] Departments of Dermatology and Microbiology, University of Pennsylvania, 1015 BRB II/III, 421 Curie Blvd, Philadelphia, PA 19104, United States
[2] Center for Cell Death, Injury & Regeneration, Departments of Drug Discovery & Biomedical Sciences and Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, SC, United States
[3] Agency for Science, Technology, and Research (A*STAR), Institute for Medical Biology, Singapore

Corresponding author: Dawson, Thomas L (thomas.dawson@imb.a-star.edu.sg)

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Introduction

Malassezia and the skin microbiome

Malassezia have been known as human skin inhabitants for over 120 years [1], and are now believed to be among the most common skin inhabitants of all warm-blooded animals [2•,3,4–8]. *Malassezia* are found on both healthy and diseased skin, and hence their role as commensals or pathogens is unclear and complex [9••,10–12,74]. *Malassezia* are basidiomycetious fungi and occupy a specific phylogenetic niche (class Malasseziomycetes, subphylum of Ustilaginomycotina) comprised almost exclusively of plant pathogens [13]. On the basis of their limited and highly specific genomic content (with loss of most carbohydrate processing and amplification of lipid and protein digestion) *Malassezia* are highly evolved for life on skin. They are limited by an inability to synthesize lipids and therefore are mainly found on sebaceous skin (scalp, face, back, breast). Other fungal skin residents such as *C. albicans* and dermatophytes are only distantly related to *Malassezia*, but through convergent mechanisms [14,15] express similar gene compliments evolved to life on skin, referred to as 'niche-specific evolution' [2•] (Table 1).

The role of *Malassezia* in health and disease remains controversial despite over a century of known disease associations [73,75,76]. Even 20 years after the realization that *Malassezia* is a genus consisting of multiple species [16] it remains unclear whether a single *Malassezia* species 'causes' skin abnormality or whether the cause is a complex interplay between multiple *Malassezia* species and even between *Malassezia* and other components of the skin microbiome [77]. Survival of *Malassezia* on skin depends on their ability to adapt to continuous niche changes resulting from the human host (i.e. sebum, sweat, immune responses, temperature, and occlusion), from the environment (e.g. humidity, temperature, or UV), and even changes in the local environment due to actions of other skin inhabitants (such as bacteria, viruses, dermatophytes, or parasites).

While the majority of research using culture-independent approaches to characterize skin microbial communities are bacteriocentric, similar approaches are available for fungal community profiling [17], with the ribosomal internal transcribed spacer (ITS) region formally adopted as the primary fungal barcode for taxonomic profiling [18]. While avoiding the growth-rate and cultivation biases of culture-based assays, one must also consider the potential biases introduced by culture-independent methods such as PCR primer bias, amplification bias, reagent contamination in low bioburden samples, and presence of rare community members [19–22]. All methods considered, surveys of the healthy human skin agree that *Malassezia* predominate at most body sites, aside from the feet [11,23–26]. However, considerable species diversity exists and is correlated with body site. For example, *M. restricta* is found predominantly on scalp and facial areas while *M. globosa* is localized to scalp, back, and groin. The hands and arms carried mixed proportions of *M. globosa*, *M. restricta*, and *M. sympodialis*. Overall, culture-dependent and -independent approaches agree that on human

Table 1

Distribution of *Malassezia* species

Species	Primary distribution	Disease associations
Human associated		
M. globosa	Skin of all humans, face, scalp, back.	Dandruff/seborrheic dermatitis, Pityriasis versicolor
M. restricta	Skin of all humans, ear, face, scalp. Domestic cats.	Dandruff/seborrheic dermatitis, Pityriasis versicolor
M. sympodialis	Skin of all humans, face, scalp.	Atopic eczema
M. furfur	Unclear. Human skin via culture, less in molecular studies. Only species found in blood and urine.	Neonatal invasive/septic infections.
M. dermatis	Rare, human skin.	Mostly unknown, reported changes in atopic dermatitis.
M. slooffiae	Rare, human skin. Occasionally animals.	Unknown.
M. arunalokei	Rare, human skin, India.	Unknown.
M. japonica	Rare, human skin, Japanese female.	Unknown, reported in atopic dermatitis.
M. yamatoensis	Rare, human skin.	Unknown.
M. obtusa	Rare, human groin, nasal vestibule, and also from animals	Unknown, reported in atopic dermatitis.
Animal associated		
M. pachydermatis	All animals, likely very diverse and species specific associations.	Healthy and diseased skin of many animals. Potential role in inhalational allergy.
M. equina	Horse	Healthy and diseased skin.
M. nana	Domestic cat, cow, horse ear	Healthy and diseased skin.
M. caprae	Goat	
M. cuniculi	Rabbit	
M. brasiliensis	Parrot (Brazil)	
M. psittaci	Parrot (Brazil)	

skin, *M. restricta* and *M. globosa* are the most commonly identified, with *M. sympodialis* a distant third. Other species are seen but infrequently. By contrast, *M. pachydermatis* is by far the most common *Malassezia* found on animal skin. It is likely that *M. pachydermatis* isolates are very diverse and may even be species specific [27].

Because of the commercial interest of multiple large consumer goods companies, the majority of data available on *Malassezia* metabolism and skin regard the human scalp and the development of dandruff/seborrheic dermatitis (D/SD) [28] and a pharmaceutical interest in atopic dermatitis (AD) and psoriasis. *M. globosa* and *M. restricta* have been shown to be the species commonly found on human scalp, and along with *M sympodialis* have available complete genome sequences and significant *in vitro* and *in situ* metabolism data [2•,9••,29,30].

The skin

The epidermis is the outermost layer of the skin and confers cutaneous barrier function while harboring diverse communities of microbes. Within the stratified, self-renewing layers of the epidermis lie a variety of appendages, including hair follicles, sebaceous glands, and sweat (eccrine and apocrine) glands. These appendages are key determinants of the cutaneous microenvironment and thus play an important role in shaping the populations of bacteria, fungi, and viruses colonizing the skin. Eccrine sweat glands provide moisture in addition to urea, chlorides, and other nutrients. The sebaceous gland, coupled with the hair follicle to form a pilosebaceous unit, secretes sebum, a lipid-rich substance that serves to emolliate and enhances the barrier properties of the skin. The pilosebaceous unit also supports niche-specific, anoxic organisms. It is therefore unsurprising that areas such as the face, scalp, chest, and back, are colonized with high proportions of *Malassezia* and *Propionibacterium* spp., which metabolize lipids in the sebum to free fatty acids. Similar to observations of bacterial skin communities [31], fungal diversity is higher before puberty [32], suggesting that sebaceous gland maturation and secretion of sebum is a key factor in restricting fungal community diversity.

The distribution of appendages, along with variable folding, thickness, and exposure, closely correlate with the microbial populations that colonize the skin, suggesting strong selection based on microenvironment [12,33••,34]. Differentiation of the site-specificity of the skin microbiota closely tracks with puberty, reflecting the maturation of the sebaceous glands, and selecting for lipophilic microbiota that utilize sebum for their nutrition. Gender, as a function of differential steroid hormone production, promotes structural and biochemical differences in the skin, which thereby also differentiate microbial populations.

The predilection of certain skin disorders for precise anatomical locations of similar biogeography suggests close interactions between the skin and its microbiota and their ability to modify skin health and disease states.

For example childhood atopic dermatitis frequently affects the flexural surfaces of the knees and elbows, and is characterized by heavy colonization and sometimes infection with *Staphylococcus aureus*. The role of fungi and specifically *Malassezia* in AD and other skin disorders is less well understood, as discussed in the next section.

Malassezia in disease

The roles of microbes in disease have historically been defined by "Koch's Postulates" [35]:

- The microorganism must be found in all organisms with disease, but not in healthy organisms.
- The microorganism must be isolated from a diseased organism and grown in pure culture.
- The cultured microorganism should cause disease when introduced into a healthy organism.
- The microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

Koch's postulates frame modern microbiology, but recent technological advances have complicated their interpretation. Modern methods opened a Pandora's Box of complexity, including 'unculturables', inter-kingdom interactions, microbe/host communication, and the concept of 'individual susceptibility'. Fungal infections and 'opportunism' complicate Koch's postulates: fungi may be commensal or symbiotic and at other times cause disease [36]. Opportunism, culture challenges, and the similarity to human cells have left research into fungal disease lagging that of bacterial infection.

Advances in treatment of chronically ill patients, the success of organ transplantation, and AIDS have resulted in a new population of immunocompromised hosts [37]. This stretches our understanding of the fungal/host interaction, and forces us as scientists into new definitions of pathogenicity. Historically, definition of pathogenicity has focused on either the host (host-centric) or the microbe (pathogen-centric). The emerging complexity of fungal/host interaction reveals that both the host and the microbe are components of pathogenicity — fungal toxins and direct fungal activities obviously cause host damage, but aberrant host responses such as hyper-inflammation, allergic sensitization, or 'cytokine storms' lead to the host damaging itself. Classification of 'pathogens' therefore requires adjustment, as is outlined in the 'Damage-Response' framework of interaction [38•,39,40]. In the damage-response framework, a 'pathogen' is defined as any organism whose presence can result in damage to the host. Hence, *Malassezia* can in this paradigm be classified as 'pathogens', and will be generally referred to as such in this review.

A majority of evidence support a causal role of *Malassezia* in hyperproliferative skin disease, specifically D/SD. Briefly, nystatin, a specific anti-fungal, was compared to neomycin or tetracycline, both specific antibacterials: removal of fungi decreased D/SD; removal of bacteria did not; removal of both was equal to an antifungal alone; and reintroduction of resistant '*P. ovale*' (likely *M. globosa*) induced D/SD [41–43]. Furthermore, there has been commercial use of many divergent materials to successfully treat D/SD, and with the exception of steroidal anti-inflammatories the only common activity is anti-fungal [44]. Thus, *Malassezia* fulfill three of four of Koch's postulates for D/SD. Only postulate 1 is unfulfilled, as all humans carry *Malassezia*. However, even Koch understood postulate 1 has exceptions, observing asymptomatic cholera carriers [45]. Finally, in susceptible individuals, numerical reduction of *Malassezia* correlates with D/SD reduction, but with no apparent correlation of absolute *Malassezia* numbers between affected and non-affected individuals [46].

Malassezia appear to interact with the human host via two — not mutually exclusive but potentially interacting paradigms: direct, via irritant pathways, such as in D/SD; and indirect, via allergic pathways as evidenced in atopic dermatitis.

Direct irritant interactions — example: dandruff and seborrheic dermatitis (D/SD)

Malassezia live in, on, or embedded in the stratum corneum, the uppermost layers of human epidermis, and the follicular infundibulum. On the skin surface they primarily interact with enucleated keratinocytes of the stratum corneum, but in the follicle infundibulum they are exposed to their required food source, sebum lipids, and as the infundibulum does not have continuous barrier properties *Malassezia* can interact directly with viable keratinocytes. Sebum is a mixture of triglycerides (TGs), fatty acids (FAs), wax esters, sterol esters, cholesterol, cholesterol esters, and squalene [47]. When synthesized and initially secreted sebum contains triglycerides and wax esters. After exposure to the environment and the skin microbiome the triglycerides and esters are broken down into constituent di- and mono-glycerides, glycerol, and FAs. Human sebum contains C16 and C18 chain length FAs, both saturated and unsaturated. There is a large excess of unsaturated chains, usually with a single double bond at C9 (oleic, OA, and palmitoleic, POA) and a small fraction of FA with two unsaturations at C9 and C12 (linoleic). The role of specific FAs becomes apparent by examining *Malassezia* metabolism.

Skin *Malassezia* secrete multiple lipases with broad spectrum activity which hydrolyzes most all triglycerides into FAs. *Malassezia*, however, have very specific nutritional requirements [48], and while the lipases are pleotropic, lack of a Δ^9 desaturase [49] leaves them able to only metabolize saturated FAs. The saturated FAs are consumed and the unsaturated FA left on the skin [50]. The

unsaturated FAs induce D/SD-like flaking both in an animal model [51] and in susceptible but not in non-susceptible individuals [52]. While the specific defect in susceptible individuals remains to be elucidated, it is of interest to note that another report [53] showed a skin barrier disruption effect from a similar dose of OA in a similar vehicle. These observations support that D/SD sufferers have an underlying skin barrier permeability dysfunction relative to non-D/SD individuals that renders them more susceptible to FA-induced barrier disruption. D/SD susceptibility may be in part determined by a permeability barrier defect, as is well established in the case of atopic dermatitis [54]. These data also explain the lack of a simple quantitative relationship between *Malassezia* and D/SD presence or severity in a general population. Integrating all available data, it appears that dandruff and seborrheic dermatitis at least in part result from a direct irritant effect resulting from OA mediated skin barrier disruption downstream from *Malassezia* lipase activity on sebum.

Indirect immune interactions: example: atopic dermatitis

As *Malassezia* reside not only on the skin surface but in upper layers of the epidermis and into the follicle infundibulum they have ample opportunity to interact with multiple components of the immune system [55,56]. It is accepted that in atopic dermatitis (AD) there is involvement of sensitization to multiple allergens [57], and as *Malassezia* reside on all humans, in contact with viable immune cells, and there is skin barrier defect in AD sufferers, it follows that AD suffers would be aberrantly exposed to *Malassezia* antigens and be susceptible to sensitization. Not surprisingly, most if not all AD suffers show at least some sensitization to *Malassezia* antigens [55]. Multiple allergens which show binding to human IgE have been described in AD from *M. furfur* and *M. sympodialis* [58,59], and the allergen genes have been found via homology in all *Malassezia* [29].

The evolved 'commensal' nature of *Malassezia* has led to a complicated co-existence with the skin immune system. As a 'foreign' microbe, it would be expected that immune cells would recognize *Malassezia* and respond as such. However, as a commensal, there must be some tolerance to *Malassezia* colonization. *Malassezia* colonize their human host shortly after birth, and they may even be recognized as self due to very early exposure from the mother [60]. *Malassezia* have been shown to elicit secretion of IL-1b, IL-6, IL-8, IL-10, TNF-α, and TGF-β from isolated keratinocytes and peripheral blood mononuclear cells (PBMC) in certain circumstances and in a species specific manner [61–64]. Specific *Malassezia* species have also been shown to reduce the expression of Il-6, Il1β, and TNFα in both resting and LPS stimulated peripheral blood mononuclear cells PBMC) [65]. Additionally, cytokine expression is different between D/SD hyperproliferative scalp and normal scalp, where the Il1α/$Il1_{RA}$ ratio [66], histamine, and TNF-α [67] are lower in 'healthy' skin. *Malassezia* lipid metabolism is a complex component of the immune response as well as the irritant effect. The closely related *Ustilago* and other plant pathogens modulate their plant host's immune system via secretion and modification of a series of oxidatively modified lipids termed 'oxylipins' which are very similar to human eicosanoids [68,69]. The hydrophobicity of the *Malassezia* cell wall correlates with the ability to induce cytokine expression [70], but removal of the lipid layers on the outer cell wall increases the production of cytokines [65]. While in total this work implicates lipid metabolism in *Malassezia*/host interaction, the studies are also complicated by the recent reclassification of *Malassezia* species and that many studies were conducted before the full extent of the genus was well characterized.

Sensitization to *Malassezia* as a cause of AD remains controversial, as some subjects clearly do [55,71,72,78–80], and other do not respond to known *Malassezia* antigens. This could be due to many factors including but not limited to: the presence of some unknown and unculturable microbe; an antigen only expressed in specific cases and not available for testing; an undetectable species in a specific niche which is not well sampled (such as the hair follicle) [81]. When considering the exposure and sensitization of AD sufferers to *Malassezia* antigens it must also be considered that it is a highly divergent genus and employment of single antigens from specific species is likely to underestimate the overall sensitization rate [55]. Hence, in AD, the commensal nature of *Malassezia* likely make them a source of constantly available allergens in close proximity to skin rendered 'susceptible' by genetic predisposition to lowered barrier function. Further investigation with specific potential antigens in specific species will be required to elucidate any effect at the species and strain level. Specific *Malassezia* IgE are absent in D/SD [10], likely due to the FA irritant effect on susceptible skin as mentioned above.

Summary

The interaction between *Malassezia* fungi and the host remains complex: often commensal, frequently pathogenic. *Malassezia* inhabit the skin of all humans, and can induce or suppress inflammatory responses in different circumstances. The relationship is also complicated by the number and diversity of *Malassezia* species and their functions, and the potential interactions with other members of the skin microbiome. What is clear is that the relationship is complex and that in certain circumstances *Malassezia* can induce host damage and hence should be recognized as 'human pathogens'.

Conflict of interest statement

Nothing declared.

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