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Malassezia: The Forbidden Kingdom Opens

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Malassezia **yeast exist on all humans and have long been associated with healthy and diseased skin. In this issue of *Cell Host & Microbe*, Sparber et al. (2019) and Limon et al. (2019) present murine models for *Malassezia*/host interaction and describe a role for *Malassezia* in inflammatory skin and gut disease.**

Over the last two decades, the human microbiome has exploded into the scientific conscience, generating tens of thousands of technical publications and patent disclosures. Although the human-associated microbial community consists of bacteria, fungi, viruses, and archaea, the vast majority of these publications have been limited to bacteria. Recently, technical advances in probing the fungal component have enabled realization of its importance, particularly in gut (Hernández-Santos and Klein, 2017). The majority of human mycobiome research has focused on skin, as fungi constitute a larger percentage of skin than gut microbiomes, representing 5%–10% of metagenomic sequences in skin (Byrd et al., 2018) versus less than 1% in gut. Also, the skin mycobiome is less complex and dominated by members of a single genus (50%–80% of eukaryotic metagenomic sequences), *Malassezia*. It is also important to note that while 5%–10% of the genomic material on skin represents fungi, *Malassezia*, at 8–10 μm, are significantly larger than bacteria (at 0.8–1.0 μm). Thus, the fungal "active biomass" is likely greater than 10% of the microbiome. Hence, *Malassezia* have been an important and under-researched segment of the human microbial community.

Malassezia were initially identified and associated with seborrheic dermatitis by Malassez in the late 19th century (Malassez, 1874). For the first century post-discovery, *Malassezia* research languished due to their fastidious nature and extremely difficult identification and a series of unfortunate nomenclature changes contributed to confusion across the technical literature (Figure 1). *Malassezia* were first cultivated in 1927 with the discovery that they require lipid supplementation. Originally thought to be a single species, in the 1950s they were renamed and reclassified based on lipid dependence and host: *Pityrosporum orbiculare* and *P. ovale* (based on shape) as lipid-dependent human skin inhabitants and *P. pachydermatis* as a non-lipid-dependent animal skin inhabitant. In 1998, *Malassezia* were discovered to consist of multiple species and their cultivation well enough described to initiate further interest and research (Guého et al., 1996). In humans, *Malassezia* colonization begins immediately after birth and until 6–12 months, supported by sebaceous secretions driven by maternal hormones. Colonization then drops and remains low until puberty, when sebaceous activity increases and provides the lipids necessary to support *Malassezia* populations.

Malassezia genomes are compact and well adapted, as evidenced by loss of some common gene families and multiplication of others. For example, living on sebaceous skin *Malassezia* have lost fatty acid synthase (FAS), Δ^9 desaturase, and $\Delta^{2,\ 3}$enoyl CoA isomerase and cannot elongate fatty acids (FAs) or degrade unsaturated FAs. *Malassezia* gene losses and gains support gathering nutrients via secretion of lipases, phospholipases, proteases, and other hydrolytic enzymes. This has been termed "niche specific evolution," as the hydrolase expression is similar to another opportunistic but unrelated human skin pathogen, *Candida albicans*, but different from the closely related *Ustilago*, whose secreted enzymes target degradation of plant-specific proteins, cutin, and waxes. Today, *Malassezia* represent a complex genus consisting of 18 diverse species and are found on all humans, the skin of all warm-blooded animals, the human gut, and now ecosystems as diverse as deep marine environments (Theelen et al., 2017). Hence, in the last decade *Malassezia* have moved from virtually unknown niche research into a key global focus area.

As inhabitants of the skin and gut, *Malassezia* must cope with perturbations that originate both from the host and from the external (including the gut lumen as "external") environment. Thus, *Malassezia* act at the interface of "self" with the external world: the skin and gut barriers. Factors including host and co-inhabitant microbes, environment, lifestyle choices (i.e., diet and product usage, hygiene), and immune activity can cause shifts leading to disease. Host susceptibility is also critical, making it necessary for mechanistic studies of fungal pathogenesis to be carried out longitudinally in susceptible hosts (Grice and Dawson, 2017). Thus, the convergence of difficult to control extrinsic factors and the complexity and variability of humans as study subjects has hampered research into function of human-associated microbial communities.

It even remains controversial whether *Malassezia* are benign commensals or pathogens. It is very likely that differing circumstances can lead to either. The interaction between fungi and the human host is complex and plastic—pathogenicity cannot be defined merely by presence or absence of a specific microbe but by the complex interplay of the environment and host susceptibility. This has led to a model of commensalism versus pathogenicity that includes both direct damage from the microbe and damage induced by the host response, termed the "damage-response framework" (Casadevall and Pirofski, 2000). Using this lexicon, *Malassezia* are

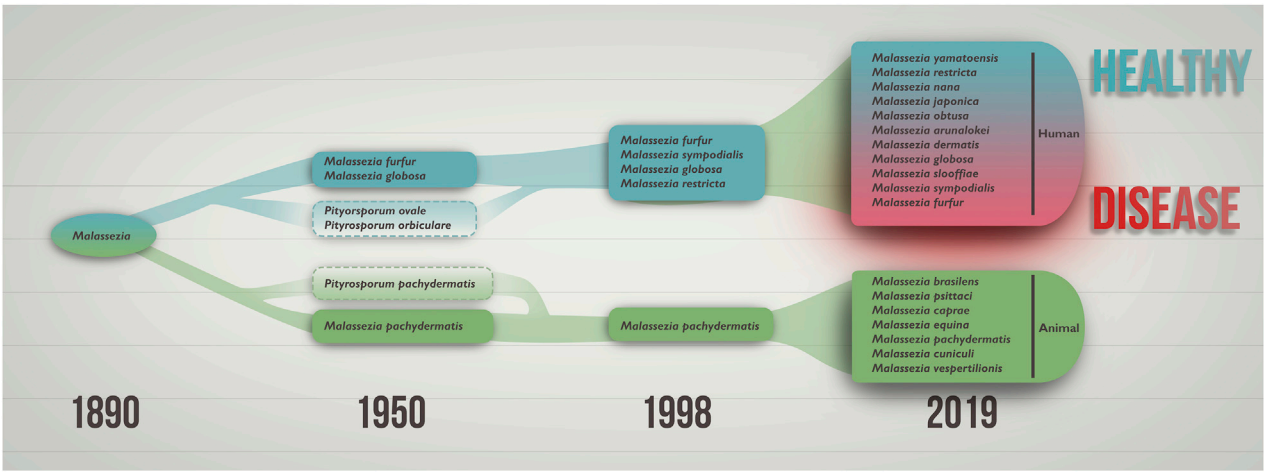

Figure 1. History of *Malassezia* Nomenclature
Malassezia were initially discovered and named as a single species in 1874. In 1950 the name *Pityrosporum* was added to describe new species on human skin, but these names are no longer in use after the 1998 discovery of multiple species based on lipid preference in culture. Currently 18 species are found on humans and animals, with variable association to pathogenicity.

classified as pathogens, with a significant body of literature linking them to skin disease. However, multiple recent publications imply that in atopic dermatitis and post-puberty adulthood, they may be protective (Theelen et al., 2017). Clearly, to progress microbial community research that drives intervention design we need new, informative models capable of dissecting the biological mechanisms underlying its function. In this issue of *Cell Host & Microbe*, two papers describe promising models of *Malassezia* infection and provide insight into the mechanisms of host/*Malassezia* interaction in both gut and skin, respectively (Limon et al., 2019; Sparber et al., 2019). Both papers show convergence of the host response with signaling through the Th17/21 axis and Card-9. This indicates a remarkably similar paradigm shared between the intestinal lumen and skin barriers.

Limon et al. (2019) have leveraged murine Crohn's disease models to define the role of *Malassezia* in gut inflammation. Two key findings previously implicated fungi in Crohn's disease: that a correlation exists with luminal gut fungi and that the most common human-associated polymorphism is within Card-9, a signaling protein essential for fungal innate immunity. However, it remained unclear which fungi were directly involved. This highlights another essential aspect of microbial community analysis: sampling. While it is much simpler to sample from feces, it is important to sample from disease-relevant sites, which in this case turned out to be intestinal mucosa. Sampling from intestinal mucosa revealed *Malassezia restricta* as the most highly correlated microbial suspect, including a strong correlation with the Crohn's Card-9 allele. Leveraging a series of murine colitis models, *Malassezia restricta* was able to induce colitis and inflammation even in gnotobiotic mice with *M. restricta* as the only eukaryote present. *M. restricta* induced proliferation and Th1/Th17 polarization in both murine- and human-derived dendritic cells more potently than *C. albicans*. This murine evidence was tied to human disease with human peripheral blood monocyte-derived dendritic cells (PBMCs) from healthy donors homozygous for either the normal or Crohn's-associated allele. PBMCs with the Crohn's-associated allele produced significantly more TNF-α and IL-8 in response to *M. restricta*, but not to *C. albicans* or *S. cerevisiae*.

Also presented in this issue of *Cell Host & Microbe* is a model for *Malassezia* infection and immune response in murine skin (Sparber et al., 2019) implicating IL17α/21 and Card-9. In this work, olive oil provided lipid supplementation and enabled multiple *Malassezia* species to colonize murine ear skin. Of the species applied, *M. pachydermatis* is the normal animal skin inhabitant, *M. furfur* are robust in culture, and *M. sympodialis* is often found on both normal and diseased human skin. *Malassezia* colonized normal murine ear skin and initiated recruitment of neutrophils and monocytes, with the colonization being cleared after 12 days. The *Malassezia* infections selectively induced the Il-17α/22 axis. Further, Rag1-deficient mice without T and B cells, and TCR$\beta\gamma$- and TCRδ-deficient mice with specific T cell defects, were unable to clear the infection. Additionally, atopic dermatitis (AD) was modeled. AD is a chronic inflammatory skin disease with clear genetic susceptibility linked to skin barrier defects, but the role of the microbial community in progression and exacerbation has remained unclear. There is even evidence that different *Malassezia* species may play different roles—some correlating with disease severity, and some being potentially protective (Chng et al., 2016). By modeling the barrier disruption of atopic dermatitis by tape stripping the ear skin, *Malassezia* dramatically aggravated cutaneous inflammation also via the Il-17/23 axis. To link the murine data to human disease, the authors assessed CCR6+ Th-17 memory T cells in normal and atopic subjects. Memory T cells were present in healthy individuals, but significantly increased in AD patients.

Together, these papers represent a step change in our ability to assess the functional role of the human mycobiome in disease. Further, the presence of multiple assembled and annotated *Malassezia*

genomes and the development of *Malassezia* genomic editing have opened the genus for further experimentation. This ability to dissect the mechanistic steps in microbe-host interactions should enable deeper understanding of the Malassezia/host relationship, faster progress into development of new potential intervention targets, and more effective future treatments.

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DECLARATION OF INTERESTS

T.L.D. is a founder and shareholder of Beauty Care Strategics and H8RS, and is a consultant for and member of the Rodan-Fields scientific advisory board.

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Setting Up Home: Fungal Rules of Commensalism in the Mammalian Gut

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***Candida albicans* is a commensal fungus of the human gut, but also causes life-threatening systemic infections. Recent studies published in *Cell Host & Microbe* (Witchley et al., 2019) and *Science* (Tso et al., 2018) provide insights into the determinants of *C. albicans* commensal fitness within the mammalian gut.**

The human gastrointestinal microbiome comprises complex communities of bacteria, fungi, and viruses. These microbes maintain their residence under the pressure posed by co-habitant microorganisms and immune surveillance. Investigation into how specific microbe-host mutualism relationships arise is highly relevant as several studies have elegantly demonstrated the important roles that the commensal microbial communities play in regulating immune homeostasis and affecting human health and disease states (Hooper et al., 2012; Limon et al., 2017).

Relative to bacteria, the fungal communities within the human gut microbiota appear less abundant and diverse. Fecal studies revealed predominance of *Candida* species, among which *C. albicans* is most prevalent (Hallen-Adams and Suhr, 2017). Importantly, *C. albicans* is responsible for >400,000 life-threatening bloodstream infections globally per year (Pappas et al., 2018), which suggests that *C. albicans* commensalism has evolved with retention of fungal virulence traits. Among these, the ability to switch from round yeast cells to long filamentous cells, called hyphae, is central to *C. albicans*' pathogenic potential, as strains defective in hyphal formation are attenuated in causing invasive infections in mice (Noble et al., 2017). The pathogenic potential of hyphae is attributed to their propensity to invade cellular and tissue barriers via expression of hyphae-associated adhesins, invasins, tissue-degrading enzymes, and toxins (Noble et al., 2017).

A "dogma" through the years has been that the yeast and hyphal *C. albicans* morphologies strictly segregate with the commensal versus the tissue-invasive states, respectively. While the contribution of yeast-to-hypha transition in pathogenicity is well recognized, less is known about the fungal factors that modulate commensal fitness within the mammalian gut. In this regard, an elegant study by Witchley et al. (2019) in this issue provides the foundation for a deeper understanding of the molecular determinants of