

Malassezia Species as Commensals in Humans

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Malassezia spp. are commensals of the skin, oral/sinonasal cavity, lower respiratory and gastrointestinal tract. Eighteen species have been recovered from humans, other mammals and birds. They can also be isolated from diverse environments, suggesting an evolutionary trajectory of adaption from an ecological niche in plants and soil to the mucocutaneous ecosystem of warm-blooded vertebrates.

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yeasts

1. Introduction

Malassezia are small thick-walled ovoid, ellipsoid or cylindrical commensal yeasts of warm-blooded vertebrates. Their genome of approximately 10 Mb is almost half the size of *Cryptococcus*, another basidiomycete of medical and veterinary importance ^{[1][2]}. The mycelial phase of *Malassezia* spp. has been observed naturally in some skin lesions and induced in specialized culture media incubated at 30 °C ^{[2][3][4][5][6]}. *Malassezia* species reproduce asexually by unipolar broad-based budding. The sexual form has not been detected, although the mating-type locus region has been identified ^[7].

An important characteristic of all *Malassezia* is their dependence on lipids for growth due to an absent fatty-acid synthetase gene and consequent inability to synthesize long-chain fatty acids. Although one species, *M. pachydermatis*, can readily grow on Sabouraud's dextrose agar (SDA), a medium without lipid supplementation, it is still lipid dependent and its growth in this medium is due to the use of lipid fractions within the peptone, a component of SDA ^{[2][8][9][10][11]}.

M. furfur was first identified on human skin in 1846 ^[12], but recently the genus has received more attention, not only because of its association with dermatological diseases in animals (dermatitis, otitis externa) and humans (pityriasis versicolor, atopic dermatitis, *Malassezia* folliculitis, seborrheic dermatitis) ^{[2][13][14]}, but also due to its increased detection in systemic infections, especially in neonates and immunocompromised patients ^{[15][16][17][18]}.

M. pachydermatis, originally thought to be part of the mycobiome in dogs and cats only, has now also been isolated from humans, production animals and from multiple exotic and wildlife species such as the sea lion, scarlet macaw, brown bear, American black bear, Eurasian badger, big anteater, common wombat, Mangaliza pig, wide-mouthed rhinoceros, Indian elephant, red fox, porcupine and coyote ^{[19][20][21][22]}.

2. Classification of *Malassezia* Yeasts

Malassezia yeasts belong to the family *Malasseziaceae*, order *Malasseziales* and class *Malasseziomycetes*. They are included in the morphologically highly diverse subdivision of *Ustilaginomycotina*, and due to their filament (hyphae) and reproduction characteristics, they are contained in the division of *Basidiomycota* [23][24][25][26].

Thus far, 18 *Malassezia* species have been identified from a variety of mammalian hosts and birds (Table 1) and further expansion of the genus is likely [27]. For species differentiation, locus analysis of specific ribosomal gene sequences, such as ITS, D1/D2, β -tubulin, chitin synthetase 2 and large subunit polymerase 2, is used. For phylogenetic stem evaluation and species delimitation, whole genome sequencing (WGS) is necessary [1][27][28][29][30][31][32][33][34][35].

Table 1. Classification of *Malassezia* by species, reference strain, hosts and phylogenetic clades.

Species	Reference Strain/GenBank Accession Genome Number	Described Hosts	Clade
<i>M. furfur</i>	CBS 14141, GCA_009938135	Human, Cat, Dog, Cattle, Pig, Goat, Elk, Horse, Sheep, Elephant, Monkey, Ostrich, Pelican	A
<i>M. brasiliensis</i> *	MA 1455	Parrot	A
<i>M. yamatoensis</i>	MY9725, GCA_001264885	Human, Cat	A
<i>M. psittaci</i> *	MA 1454	Parrot	A
<i>M. obtusa</i>	CBS 7876, GCA_001264985	Human, Cat, Dog, Goat, Horse	A
<i>M. japonica</i>	CBS 9431, GCA_001264785	Human, Cat	A
<i>M. vespertilionis</i>	CBS 15041, GCA_002818225	Bat	A
<i>M. globosa</i>	CBS 7966, GCA_001264805	Human, Cat, Dog, Cattle, Goat, Horse, Sheep,	B

Species	Reference Strain/GenBank Accession Genome Number	Described Hosts	Clade
		Cheetah	
<i>M. restricta</i>	CBS 7877, GCA_001264765	Human, Cat, Dog, Cattle, Goat, Horse, Sheep	B
<i>M. arunalokei</i>	CBS 13387, GCA_020085095	Human, Dog	B
<i>M. sympodialis</i>	ATCC 42132, GCA_001264925	Human, Dog, Cat, Pig, Cattle, Goat, Horse, Sheep, Chicken	B
<i>M. dermatis</i>	CBS 9169, GCA_001264665	Human, Cat	B
<i>M. caprae</i>	CBS 10434, GCA_001264625	Goat, Horse, Human	B
<i>M. equina</i>	CBS 9969, GCA_001264685	Horse, Cattle	B
<i>M. nana</i>	JCM 12085, GCA_001600835	Cat, Dog, Cattle, Horse	B
<i>M. pachydermatis</i>	CBS 1879, GCA_001264975	Human, Dog, Cat, Pig, Goat, Rabbit, Various exotic and wild mammals, Birds (Thraupidae, Macaw)	B
<i>M. cuniculi</i>	CBS 11721, GCA_001264635	Rabbit	C
<i>M. slooffiae</i>	CBS 7956, GCA_001264965	Human, Cat Cattle, Sheep, Pig, Goat, Horse	C

[27]

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3. *Malassezia* Species in the Environment and Possible Vectors

Although first isolated from the skin of humans, followed by other warm-blooded vertebrates, recent data have shown that *Malassezia* species have a much broader spectrum of ecological diversity than originally thought [36][37][38]. These yeasts have now been isolated from a range of environments, including marine water, anoxic oceans, hydrothermal vents, deep-sea to high arctic marine sediment and Antarctic soil [36][39][40][41][42][43][44][45][46][47][48][49]

[50][51][52]. *Malassezia* species also dominate the mycobiome of marine invertebrates, such as sponges and corals, and have been identified in healthy and diseased marine algae [36][53][54]. In addition, *Malassezia* species have been isolated from soil nematodes, cone-snails, olive fruit-flies and orchid roots [55][56][57][58]. A potential role for nematodes and flies as vectors for *Malassezia* has been speculated [55][58][59][60].

It is now apparent that *Malassezia* species are among the most widespread fungi on Earth [36][37][38]. Their evolutionary trajectory involves adaptation from an ecological niche in plants and soil to the mucocutaneous ecosystem of animals [36][37][38]. This has been facilitated by the loss of complex carbohydrate metabolism genes (glycosyl hydrolase encoding) and a genus-wide gain of lipid hydrolases including lipases, phospholipases and acid sphingomyelinases that are required to degrade and use skin- or mucosa-associated lipids [1][36][37][38].

4. *Malassezia* Species and Their Role as Commensals in Humans

Twelve *Malassezia* species have been isolated from human skin [6][16][34][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75] (Table 1). *Malassezia arunaloeki* is the only species isolated from humans that has not been isolated from animals, with the exception of dogs [74][76].

Malassezia species colonization of the skin starts directly after birth, increases until around 12 months of age, and then remains relatively static until puberty, when another significant quantitative increase in colonization occurs, associated with increased sebaceous gland activity and changes in the lipid composition of the skin [6][77]. After puberty, *Malassezia* species comprise 50 to 80% of the human mycobiome [78][79][80][81]. The limited data currently available about cutaneous mycobiomes in preterm and term neonates shows that *Malassezia* species distribution on the skin of neonates and children varies between studies, but *M. globosa*, *M. furfur*, *M. sympodialis* and *M. restricta* are the most prevalent species described [14].

In contrast, *M. restricta* and *M. globosa* dominate the mycobiome of both healthy and diseased skin in adult humans, followed by *M. sympodialis*, albeit at a much lower frequency than the former two [1][62][69][82][83][84][85][86][87][88][89][90][91][92]. *M. furfur* can be common at certain body sites (e.g., toe-web space) in healthy individuals but is not a dominating species overall. Instead, this species is more frequently isolated from skin diseases, such as psoriasis vulgaris and pityriasis versicolor [1][5][73][90][91][92][93][94].

Climate and ethnicity also impact the carriage of *Malassezia* species [95][96]. In a study by Leong et al. in 2019, people in Singapore of four different ethnicities (Chinese, Malay, Indian and Caucasian) carried a higher number of *Malassezia* species and showed greater species diversity and evenness than Caucasians in Switzerland. The predominant species (isolated by culture from the skin of the side of the nose) in the latter were *M. restricta* and *M. sympodialis*, while *M. globosa* was absent. In contrast, sampling from the same site in the four ethnic groups in Singapore showed *M. globosa*, *M. furfur* and *M. restricta* were the dominant species. Caucasians from the two locations showed different species distributions, with *M. restricta* being twice as common among those in Singapore, while *M. globosa* was absent in Swiss Caucasians. The same study associated the lower temperature

and humidity of Switzerland compared to Singapore with a lower positive culture rate and lower species diversity [96] (Figure 1). From other studies, it can be concluded that *M. restricta* plays a dominant role as a skin commensal in Europe, whereas *M. globosa* comparatively dominates in Asia [13][97].

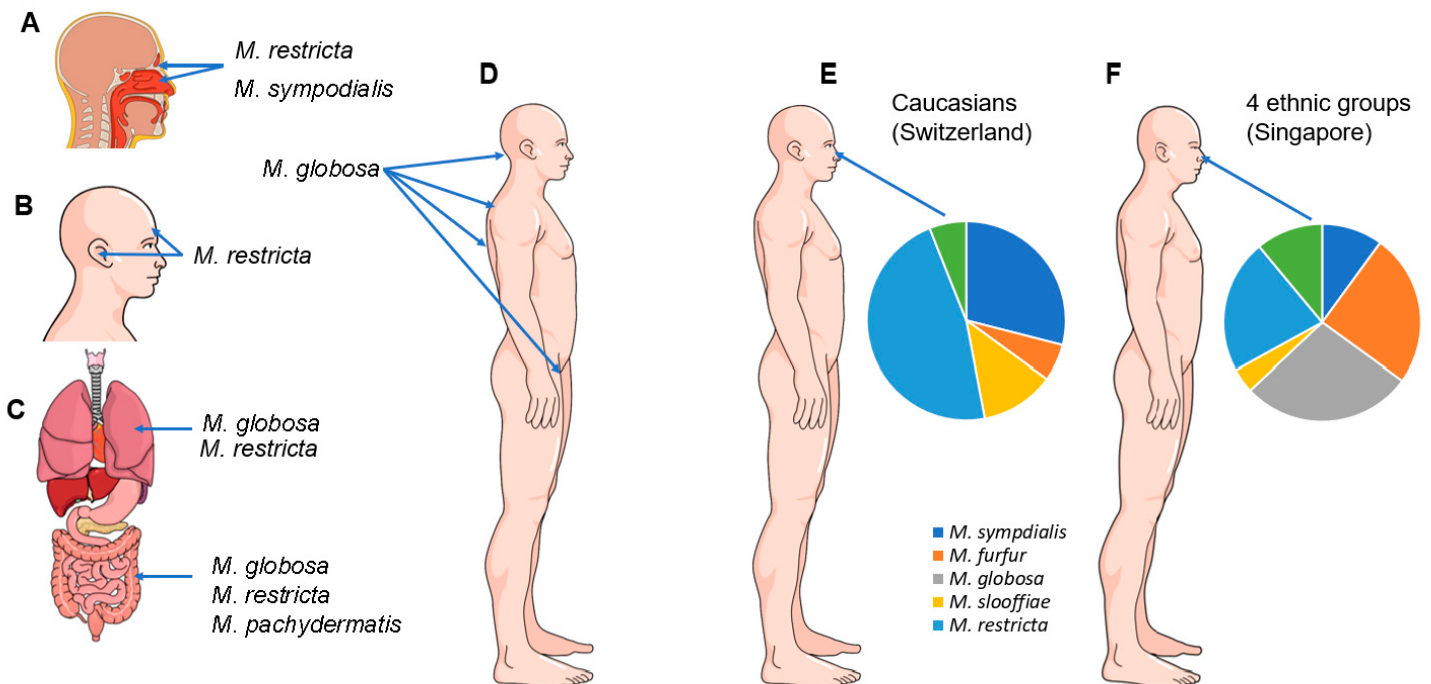


Figure 1. Predominant *Malassezia* species found as commensals in the sinonasal cavity (A), on the skin of the forehead and external ear canal (B), in the lungs and gastrointestinal tract (C) and on the skin of the occiput, back and groin (D). The relative diversity of *Malassezia* species found in healthy skin is shown in (E,F). The predominant species isolated from the culture of the skin on the side of the nose of Caucasians in Switzerland were *M. restricta* and *M. sympdialis*, while *M. globosa* was absent. In contrast, sampling from the skin of the noses of 4 ethnic groups (Chinese, Malay, Indian and Caucasian) in Singapore overall revealed *M. globosa*, *M. furfur* and *M. restricta* to be the dominant species [96].

Several studies have shown that sex and body site also influence the species of *Malassezia* species present on the skin and their abundance [1][81][89][92][98][99][100]. Site-specific species include *M. restricta*, which favors colonization of the external ear canals, retroauricular crease and forehead and *M. globosa*, which is most commonly isolated from the back, occiput and groin [81][101].

A Japanese study in 2010 quantified *Malassezia* colonization of the skin of the cheek using real-time PCR and determined associations with gender and age in 770 healthy individuals [100]. Total *Malassezia* DNA in males stayed constant from age 0 until around 9 years of age, with a progressive increase each year thereafter until the age of 16 to 18. In females, total *Malassezia* DNA increased until the age of 12, decreased between the ages of 19 and 22, and then increased again between the ages of 30 and 39. In both genders, there was a gradual decrease in *Malassezia* species abundance over the course of life. Overall, males tended to have more abundant *Malassezia* DNA than females, and *M. globosa* and *M. restricta* were the dominant species for both for all ages.

Malassezia species carriage at different skin locations was investigated using culture-based methods. No significant differences between the genders were found. While *M. restricta* dominated the scalp and *M. sympodialis* dominated the trunk, *M. globosa* was about equally common at both locations [102].

Other factors that may influence the colonization of *Malassezia* species include host factors (immune response, body secretion, skin occlusion), other skin inhabitants (e.g. parasites, other microbes) and environmental parameters, including exposure to ultraviolet light [97]. Even the birth process itself has a significant impact. If a baby is born via natural delivery, its skin microbiota resembles the mother's vaginal communities, but if delivered via caesarian section, it represents the mother's skin surface population [103][104][105][106][107]. In addition, vaginal birth is associated with a higher abundance of *Malassezia* [108][109].

Malassezia species were previously thought to be commensals of the skin only. Although the skin is the primary ecological niche, more recent data demonstrate that these yeasts also colonize the mucosa of the sinonasal and oral cavities, as well as the gastrointestinal and lower respiratory tract [110][111][112][113][114][115]. *Malassezia* species are dominant members of the mycobiome of the sinuses, with *M. restricta* and *M. sympodialis* most frequently detected [116]. *Malassezia* also comprise 30% of the gastrointestinal mycobiome, with three species detected—*M. globosa*, *M. restricta* and *M. pachydermatis* [117]. The fungal burden in the lungs of healthy people is relatively low. In one study, using a metagenomic approach, the lung mycobiome was characterized by a high proportion of basidiomycetes, including *M. restricta* and *M. globosa* [118], while in another ascomycetes, including *Candida* species, were most abundant [119] (Figure 1).

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