*Medical Mycology* June 2007, **45**, 287–303

informa
healthcare

Review

# Update on the genus *Malassezia*

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*Malassezia* yeasts are commensals of normal human skin, but also cause pityriasis versicolor, seborrhoeic dermatitis and evidence is accumulating that they play a significant role in atopic eczema/dermatitis syndrome (AEDS; formerly atopic dermatitis). The taxonomy of the genus has changed considerably and is likely to change more in the future. Our understanding of the interaction between *Malassezia* and the host demonstrates that it has the paradoxical ability to both stimulate and suppress the immune response directed against it and there is a fine balance in its existence at the interface between commensalism and pathogenicity.

**Keywords** *Malassezia*, atopic eczema/dermatitis syndrome, immune system

## Aim

The aim of this review is to provide an overview of the species within the genus *Malassezia,* their role in human disease and recent developments in our understanding of their interaction with the host immune system.

## Physiology and biology

All of the species within the genus, with the exception of *Malassezia pachydermatis,* are lipid dependent due to an inability to synthesize $C_{14}$ or $C_{16}$ fatty acids *de novo* [1]. Because of this inability, the organisms require an external source of lipid and for many years this confounded the ability of investigators to culture them *in vitro*. Their lipid dependent nature was first reported by Benham and she noted that they needed a lipid supplement to grow [2]. Another source of confusion in early studies was the dimorphism of the species. Many investigators believed that the yeast phase (denoted by *Pityrosporum*) and the mycelial phase (denoted by *Malassezia*) were different organisms, and it was not until 1977 when three groups showed that the phases could be interconverted [3–5] that the dimorphism of the organism was recognized. Various factors have been shown to induce the conversion, including glycine [3], cholesterol [4] and squalene [6], although not all species and strains appear able to undergo this phase transition [6]. This recognition of the dimorphism was followed in 1986 by the unification of the naming of the genus with all species and growth phases named *Malassezia* [7]. *Malassezia* species are biochemically relatively inert and possess a very thick cell wall [8] which is surrounded by a lamellar or 'capsular-like' layer which contains lipids [9] and can be removed with solvents.

Species of *Malassezia* produce a range of metabolites, including gamma lactones, that give the organisms their characteristic fruity smell [10]. When grown in the presence of oleic acid, azelaic acid is produced in addition to other dicarboxylic acids [11]. Azelaic acid is inhibitory to neutrophils, causing decreased production of reactive oxygen species [12] and is a competitive inhibitory of tyrosinase, a key enzyme in melanogenesis [11], leading to speculation that azelaic acid may be important in the skin pigmentation changes seen in pityriasis versicolor. Mayser *et al*. [13] described the production of fluorochromes and pigments by *Malassezia* species in cultures where tryptophan was the main nitrogen source. These pigments gave the organism protection from both UVA and UVB radiation *in vitro* [14,15] and were characterized as indole alkaloids [16]. Pityrialactone, one of the alkaloids, may be responsible for the fluorescence of lesions of pityriasis versicolor under Wood's light, as it shows fluorescence of a

Received 1 September 2006; Accepted 2 January 2007
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DOI: 10.1080/13693780701191373

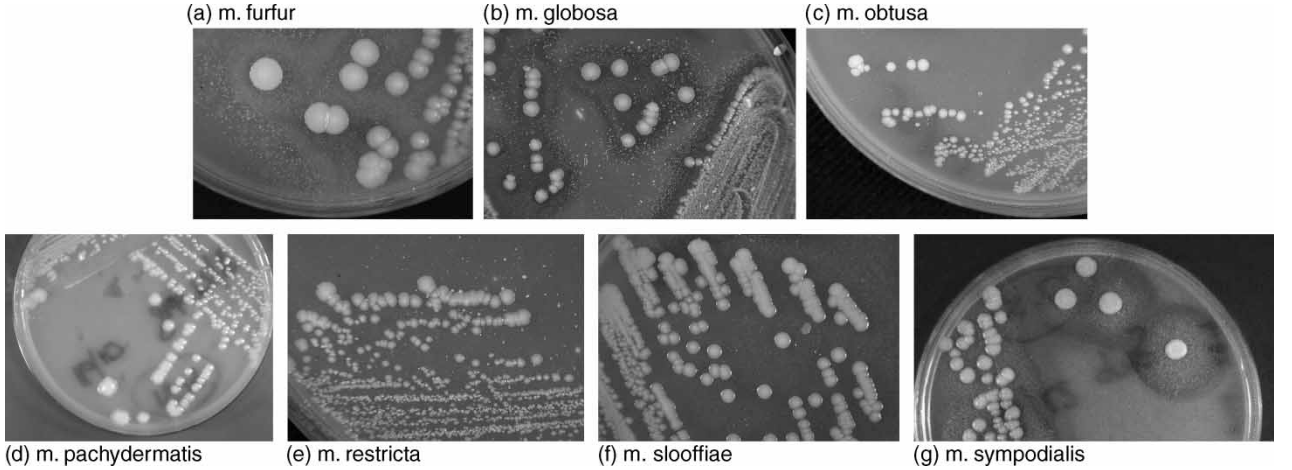


**Fig. 1** The colonial morphologies of the common species of *Malassezia* as seen when grown on Leeming and Notman agar at 34°C for 7 days

similar colour *in vitro* [17]. Further properties of these alkaloids also seem to correlate with other clinical signs of pityriasis versicolor. Malassezin induces apoptosis of melanocytes, leading to decreased melanin synthesis which may contribute to the depigmentation of lesions of pityriasis versicolor in some patients [18]. Pityriarubins are inhibitors of the respiratory burst and have been suggested as being partially responsible for the limited inflammatory response seen in lesions of pityriasis versicolor [19].

For organisms such as *Malassezia* that live as commensals, protective mechanisms against host defences are very important in enabling them to survive in their normal environment. Recently, the presence of melanin-like pigment in the yeast *in vitro* and *in vivo* in pityriasis versicolor and seborrhoeic dermatitis lesions has been reported [20]. Melanized fungi are less susceptible to reactive oxygen species generated during immunological responses and production of melanin is known to be an important virulence factor for *Cryptococcus* [21]. *Malassezia*, another pathogenic basidiomycetous yeast, may therefore employ a similar mechanism of protection against the host defences.

*Malassezia* species produce a wide range of enzymes, including lipases, phospholipases and a hydrolase. The lipases are essential in providing the lipids required for growth and recently the gene encoding an extracellular lipase in *M. furfur* was expressed and the lipase characterized [22]. The gene, MfLIP1, encoded a protein with a molecular mass of 54.3 kDa and a pH optimum of 5.8 with hydrolytic activity against Tweens, often used in culture media as a lipid source. Flanking MfLIP1 was a gene encoding catalase, which may also be secreted by the organism. Another enzyme with lipolytic activity and homology to the lipases of *Candida* has been described in *M. pachydermatis* [23]. The enzyme had a predicted molecular mass of 48 kDa, was produced when the organism was grown without lipids in the culture medium and contained a consensus sequence which is conserved among lipolytic enzymes. The pH optimum was 7.5 and the enzyme was most active against substrates with a carbon chain length of $C_8$.

*In vitro* Phospholipase $A_2$ activity by *Malassezia* is able to release arachidonic acid from epithelial cells which has been postulated as an initiator of the inflammatory response in the skin seen in *Malassezia*-associated diseases [24].

## Taxonomy

The taxonomy of *Malassezia* has undergone extensive revisions in the last 10 years and is still in a state of flux, with a new species described but not formally recognized (*M. equi* [25]) and other species demonstrating significant diversity [26,27]. Eichstedt was the first to describe a fungus associated with lesions of pityriasis versicolor in 1846 (cited by [28]), although it was not until 1853 that the organism was named *Microsporon furfur*. The yeast phase was named *Pityrosporum*, with three species recognized – *P. orbiculare*, *P.ovale* and *P. pachydermatis*, whilst the mycelial phase was named *Malassezia furfur*. In 1986, the synonomy of these organisms was recognized and the name *M. furfur* formally accepted for the lipid-dependent organisms [7]. In 1990, Simmons & Gueho described a new species, *M. sympodialis*, isolated from an AIDS patient suffering from tinea capitis [29]. Variations in the colonial morphology and characteristics of isolates of '*M. furfur*' led to the description of

**Table 1** Synonyms of *Malassezia* species

| Currently accepted species | Previously used synonyms |
|---|---|
| *M. globosa* [34] | *Pityrosporum orbiculare* [31]; *M. furfur* Serovar B [30] |
| *M. slooffiae* [34] | *Pityrosporum ovale* Form 1 [31] |
| *M. obtusa* [34] | *P. ovale* Form 2 [31] |
| *M. sympodialis* [34] | *M. sympodialis* [29]; *M. furfur* Serovar A [30]; *P. ovale* Form 3 [31] |
| *M. furfur* | *M. furfur* [31] |
| *M. restricta* [34] | *M. furfur* Serovar C [30] |
| *M. pachydermatis* [34] | *P. pachydermatis* [31]; *M. pachydermatis* [30] |
| *M. dermatis* [35] | – |
| *M. japonica* [36] | – |
| *M. nana* [37] | – |
| *M. yamotoensis* [38] | – |
| (*M. equi* [25]) | – |

three serovars [30] and the continued recognition of different forms of the organism by several groups [31,32]. In an attempt to resolve this confusion, Guillot & Gueho collected representative isolates of all the variants and sequenced the large subunit rRNA and compared the DNA/DNA reassociation [33]. Their results demonstrated that there were indeed significant differences in the variants and these were sufficient to merit their separation into distinct species. The following year, they described and named 7 species of *Malassezia: M. furfur, M. sympodialis, M. obtusa, M. globosa, M. restricta, M. slooffiae* and *M. pachydermatis* [34]. Interestingly, in their initial work five new species were differentiated, although only four of them were subsequently named, hinting at the possibility that other species existed. Subsequently, other species of *Malassezia* have been described, including *M. dermatis* [35], *M. japonica* [36], *M. nana* [37], *M. yamotoensis* [38], and *M. equi* although the latter has not been formally recognized as a species [25]. The changes in taxonomy make comparison of current and previous studies difficult, although Table 1 defines the relationship between old and new classifications, as far as is currently possible.

Many molecular methods have now been developed to examine the taxonomy of the genus and most have confirmed the presence of seven distinct species corresponding to those described by Guillot [33] and more recently the 11 species currently recognised in the genus [39]. Methods such as karyotyping [40]; sequencing of the chitin synthase 2 gene [41], the large subunit (LSU) of mitochondrial rRNA [42], the LSU of the rDNA or the ITS region [43]; PCR of the LSU of rRNA and digestion with restriction enzymes [44]; amplified fragment length polymorphism and denaturing gradient gel electrophoresis [45] have all defined seven genetically distinct groups. Several studies have also found that within a currently accepted species there are subgroups (2 [40], 4 [45] or 8 [43] in *M. furfur*; 4 in *M. sympodialis* [27]; 4 in *M. pachydermatis* [26]) and it is likely that this variation within the species may result in the separation of some of the variants and the creation of new species in the future.

## Culture, identification and preservation of *Malassezia* species

Despite many earlier attempts, the first successful culture of *Malassezia* is thought to have been achieved by Panja in 1927 [46]. The recognition that an external source of lipid was required paved the way for the development of specific media to recover the organism. Many media have been described and they use a range of lipid sources. The simplest medium is Sabouraud's agar overlaid with sterile olive oil, but this medium does not allow enumeration of colonies or detailed examination as the colonies tend to coalesce. Several other media, including Dixon's medium, (containing Tween 40 and glycerol mono-oleate, [47]) and Leeming and Notman agar (containing Tween 60, glycerol and full fat cow's milk, [48]) have been developed as selective media for *Malassezia* species. Figure 1 shows the colonial morphology of some of the species of *Malassezia* on Leeming and Notman agar. Recently with the recognition of new species of *Malassezia* it has become apparent that some media may be more effective at recovering certain species than others and this selectivity will obviously impact on recovery data reported by different groups. What is also apparent is that, as yet, there is still no single medium that is able to reliably recover and maintain all the species of *Malassezia* described so far.

When the re-classification of the *Malassezia* genus occurred in 1996, sequencing of the large subunit

rRNA and DNA/DNA reassociations were used, but biochemical methods were subsequently published [49]. These were largely based on the micromorphology of the yeasts and the ability of the species to use different Tweens as lipid sources. Since then, modifications and additions to the biochemical methods have been reported that allow better differentiation between similar species. The characteristics of the 11 currently recognized species of *Malassezia* and their reactions in the various identification tests are detailed in Table 2.

The most recent method developed for identification of *Malassezia* species is a bead suspension array that uses species and group specific probes analysed by flow cytometry [50]. The system was initially developed using pure cultures of all 12 currently known species and an unnamed species and is now being modified to detect species direct from clinical material. However, due to its complexity and expense it is unlikely to be useful in a routine setting.

Although identification of *Malassezia* species can be performed, it is important to consider is when it is appropriate to do so. For most routine clinical mycology laboratories there is little need to speciate the isolates that may be recovered from superficial samples. Although it is of epidemiological interest to determine the species of *Malassezia* associated with diseases, this is beyond the scope of most laboratories in a routine clinical setting. For pityriasis versicolor, the microscopic appearance is pathognomonic, and isolation of *Malassezia per se* does not confirm the diagnosis of any of the conditions with which it is associated. However, for samples from sterile and deep sites, culture and identification should be performed.

Because of the time it takes to culture *Malassezia* (5–14 days, dependent on the species) and the realization that no single medium can reliably recover all the species, several groups have developed methods for the molecular analysis of *Malassezia* directly from the skin without prior culture. Gaitanis *et al*. [51] took skin scales from 11 patients (with seborrhoeic dermatitis or pityriasis versicolor), extracted the DNA and used PCR and RFLP analysis to determine the species present. Five of the samples yielded DNA; *M. restricta* and *M. sympodialis* were detected in the samples from patients with seborrhoeic dermatitis and *M. globosa* was detected from the patients with pityriasis versicolor. In a similar study of 49 patients with pityriasis versicolor, *M. globosa* and *M. restricta* were detected from 94% of patients, with other species detected in less than 35% of patients [52]. In another non-culture based study of the scalp flora of patients with dandruff, swabs were taken from the scalps of 70 patients, DNA extracted directly and terminal fragment length polymorphism analysis involving fluorescent nested PCR of the ITS1and ITS2 region performed [53]. *M. restricta* and *M. globosa* were found to be the most prevalent species. *M. obtusa* and *M. slooffiae* were found less commonly and *M. furfur* and *M. pachydermatis* were not detected in any patient. A study using real time PCR to analyse the lesional flora of 34 patients with atopic eczema/dermatitis syndrome (AEDS) produced a similar spectrum of species, with *M. globosa* and *M. restricta* detected most commonly, with higher population densities on the head and neck than on the trunk or limbs [54]. Thus molecular methods, despite removing the need to culture *Malassezia* species have produced largely similar results to previous culture-based studies, which also found *M. sympodialis, M. globosa* and *M. restricta* to be the commonest species found on human skin [55]. Most recently, the *Malassezia* species present on psoriatic lesions were found not to differ from those on normal skin [56]. The quest to associate particular species of *Malassezia* with a specific disease has been pursued using many different methods and by many different groups. Although some groups have suggested an association, most studies have shown broadly similar species on healthy and diseased skin. Currently, we do not know whether the pattern of species on healthy skin changes temporally or varies between sites over time, so studies that take a 'snapshot' of the flora at a given time are unlikely to reveal the whole picture. In both culture and non-culture based studies, it is essential that robust sampling methods are used, as the results are only as representative as the collection of the initial sample allows.

One of the problems associated with working with *Malassezia* is the difficulty of preserving isolates, with certain species being particularly fastidious. In general, *M. sympodialis, M. pachydermatis* and *M. furfur* tend to remain viable during storage, whilst *M. globosa, M. restricta* and *M. obtusa* are very difficult to maintain *in vitro* [34]. Crespo *et al*. carried out a study examining different preservation methods and found that storage at -80°C was the most reliable method [57], with a final assessment of viability at 18 months after preservation. However, only four strains of the most fastidious species were included and results for 'lipid-dependent' species were reported together, so it is likely there are variations in survival between the different species not detected in this study.

## Commensalism

*Malassezia* species form part of the normal cutaneous commensal flora of humans and animals. In humans

**Table 2** Properties and characteristics of the 11 currently recognized species of *Malassezia*[a]

| Characteristic or test | *M. furfur* | *M. sympodialis* | *M. globosa* | *M. restricta* | *M. slooffiae* | *M. obtusa* | *M. dermatis* | *M. japonica* | *M. nana* | *M. yamotoensis* | *M. pachydermatis* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Colony morphology and texture | Smooth, soft, friable | Flat, smooth, shiny, soft | Rough, brittle | Smooth, hard, brittle | Finely folded, brittle | Smooth, flat, sticky | Convex, entire or lobed edge | Dull, wrinkled, entire or lobed edge | Smooth, convex, dull, soft | Shiny, wrinkled, entire or lobed edge | Convex, smooth, soft, friable |
| Cell size and shape* | 6 μm S, O, E | 2.5–5 μm O, G | 6–8 μm S | 2–4 μm S, O | 1.5–3.5 μm C | 4–6 μm C | 2–10 μm S, O, E | 2–7 μm S, O, E | 1.5–3 μm O, G | 2–7.5μm O, E | 2.5–4.0 μm C. |
| Bud pattern | Broad base | Sympodial | Narrow base | Narrow base | Broad base | Broad base | NS | Sympodial | Narrow | Narrow | Broad base, distinct bud scar |
| % G+C | 66.4 | 62.2 | 53.5 | 59.9 | 68.7 | 60.7 | 60.4 | 60.4 | NS | NS | 55.6 |
| Catalase reaction | + | + | + | − | + | + | + | + | + | + | V |
| Growth at 37°C | Good | Good | Poor | Poor | Good | Poor | Good | Good | Good | Good | Good |
| Ability to split aesculin | − | + | − | − | − | + | − | NT | − | NT | V |
| Growth with Tween 20 | + | − | − | − | + | − | + | − | V | + | + |
| Tween 40 or 60 | + | + | − | − | + | − | + | 40: v 60: + | + | + | + |
| Tween 80 | + | + | − | − | − | − | + | − | V | + | + |
| Cremophor EL | v | − | − | − | − | − | + | NT | − | NT | V |
| Cremophor S9 | + | + | − | − | + | − | NT | NT | NT | NT | NT |
| Precipitate on Dixons agar | − | + | + | NT | − | − | + | NT | + | NT | NT |
| Colony on modified CHROMagar [156] | Pink, smooth, raised centre | Purple, smooth | Light pink, smooth | Dark purple, rough | Light pink, rough | Dark purple, smooth | NT | NT | NT | NT | Light purple, smooth |

[a]Data compiled from references [34–36,38,49,156–161].

*S = Spherical; O = Oval; G = Globose; E = Ellipsoidal; C = Cylindrical.

NT = Not tested; NS = Not stated; v = variable results; + = positive; - = negative.

**Table 3** *Malassezia* species isolated from healthy skin on different body sites reported from different countries (% patients colonized with each species)

| Country | Site | *M. glob* | *M. glob+other species* | *M. sym* | *M. restricta* | *M. furfur* | *M. sloof* | Other species | Negative cultures |
|---|---|---|---|---|---|---|---|---|---|
| Spain [162] | | **71** | | 16 | 6.5 | | | | |
| Korea [163] | Chest | **59.5** | | 35.1 | 13.5 | 2.7 | 13.5 | 2.7 | |
| Korea[164] | | **49** | | 10 | 21 | 4 | 0 | | 16 |
| Spain [162] | | **62** | | 38 | 0 | | | | |
| Korea [163] | Back | **48.6** | | 37.8 | 8.1 | 5.4 | 16.2 | 0 | |
| Japan [93] | Trunk | **51** | | 25.7 | | | | | 22.8 |
| Spain [162] | | 33 | | 13 | **48** | | | | |
| Korea [163] | Scalp | 27 | | 5.4 | **51.4** | 0 | 8.1 | | |
| Korea [164] | | 22.5 | | 0 | **39** | | 1.5 | | 37 |
| Japan [93] | | **15.5** | 6.8 | 12.6 | 2 | 6.8 | 1 | 4.9 | 38 |
| Spain [61] | Shoulders | | | **41.7** | | | 5.2 | | 53.1 |
| Spain [61] | | **12.5** | | 2.1 | | | | | 85.4 |
| Korea [163] | Forehead | 29.7 | | 10.8 | **56.8** | 0 | | 2.7 | |
| Korea [164] | | 22.5 | | 1 | **55** | 1.5 | 0 | | 20 |
| Japan [93] | Face | 7.8 | | 8.7 | 1 | **10.7** | 1 | | 46 |
| USA [56] | Arms | 23.5 | | 15 | **40.4** | 0.1 | | | |
| Tunisia [165] | | **8** | **8** | 5 | | 4 | | | 69 |
| Spain [69] | | | | **71** | | | | | 29 |
| Canada [70] | Not stated or | 30.6 | | **47.8** | 2.9 | 8.1 | 7.7 | 2.9 | |
| Canada [166] | multiple sites | 25 | | **80** | | | | | |
| Sweden [94] | | 12 | | **69** | | | 4 | 15 | 16 |
| Japan [92] | | 44.4 | | **50** | 61.1 | 11 | 0 | 0 | |
| Iran [167] | | **41.7** | | 25 | 3.3 | 23.3 | 6.7 | | |

The figures for the predominant species are highlighted in bold.

they are associated with the sebum-rich areas of the body, including the trunk and the head region, with population densities peaking between 20–45 years [58]. Many studies have looked at the distribution of the recently defined species on normal skin, and conflicting results have emerged, with different species predominating in different countries. Table 3 summarizes the species isolated from different body sites in different countries. Although these differences may be partly explained by the sampling methods and culture media used, there are probably genuine geographical variations, with the effects of ethnicity and differing diets reflected in the predominance of different species on the skin of individuals in different parts of the world. The species most commonly detected on normal human skin are *M. sympodialis*, *M. globosa* and *M. restricta*, regardless of the culture medium used, the method of sample collection, or the country of study.

## *Malassezia*-associated disease in humans

*Malassezia* has been associated with a range of cutaneous and systemic diseases, including pityriasis versicolor, seborrhoeic dermatitis, folliculitis, atopic eczema/dermatitis syndrome (AEDS), catheter-related fungaemia, peritonitis and meningitis [59] (Table 4).

Pityriasis versicolor presents as scaly hypo- or hyperpigmented lesions usually on the trunk and back of affected individuals [60], although in extensive disease lesions may occur on almost any body site. The disease occurs mainly in adults aged 20–50 years, is more common in tropical climates and recurs frequently due to the commensal nature of *Malassezia*. Microscopic examination of scrapings from lesions demonstrates a characteristic 'spaghetti and meatballs' appearance, with both yeast and hyphal forms present due to the phase transition from yeast to mycelium seen in this disease. Many explanations have been suggested for the pigmentary changes in pityriasis versicolor lesions, including the production of azelaic acid and several tryptophan metabolites by *Malassezia* which can interfere with melanization, but as yet the exact mechanism remains uncertain. Studies of the flora on lesions has yielded conflicting results, with some authors stating that *M. globosa* is the causative species [61,62], whilst others have found *M. sympodialis* to predominate [63] (see Table 4). As with the studies on normal skin, sampling methods and the culture media used for these studies will influence the species recovered and hence may affect the results.

Seborrhoeic dermatitis (SD) is an inflammatory condition occurring on the scalp, face and trunk in around 2–5% of the healthy population, but in up to 70–80% of patients with untreated AIDS [64]. It is a chronic condition with exacerbations often triggered by stress and dry environments. The improvement of SD (and the related condition, dandruff) by treatments directed against *Malassezia* supports the role of the yeast in these conditions, although other factors such as impaired barrier function are also thought to be important [65]. The densities of *Malassezia* present on lesion and non-lesional skin have been studied with some groups finding increased densities on lesions [66], whilst others found no difference [55,67,68]. The species of *Malassezia* associated with the lesions have also been examined and a complex picture has emerged with *M. restricta, M. globosa, M. furfur, M. sympodialis* and *M. obtusa* all recovered from significant numbers of patients in different studies [53,69–72] (see Table 4). Recently, it was shown that application of oleic acid to the scalps of susceptible individuals induced flaking similar to dandruff [73] suggesting that the pathogenesis of SD is multifactorial and that there is no simple relationship either between the number of *Malassezia* present or the particular species and initiation of disease.

Folliculitis associated with *Malassezia* was first reported in 1969 in a patient taking tetracycline [74]. The condition presents as follicular papules and pustules surrounded with an erythematous area, occurring on the trunk, neck and face. Since 1969 it has been described in various patient groups, including adults in an intensive care unit [75]; bone marrow [76], heart [77] and renal [78] transplant recipients; pregnant women [79,80]; patients with AIDS [81], Hodgkins disease [82] and Down's syndrome [83]. *M. restricta* and *M. globosa* have been reported to be associated with folliculitis in a study of 20 patients in Korea [84].

AEDS is a multifactorial skin disease where chronic inflammation is triggered by various allergens and undergoes cycles of exacerbation and remission [85]. Micro-organisms of the cutaneous flora are known to contribute to these exacerbations in many patients and two lines of evidence implicate *Malassezia* in the inflammation and exacerbations associated with AEDS. Firstly, AEDS lesions of the head and neck region improve after antifungal therapy. In 1983, Clemmensen and Hjorth found that patients experienced improvement of their disease after 4 weeks oral therapy with ketoconazole [86], a finding which many subsequent studies have confirmed [87–91]. The second line of evidence is that AEDS patients have increased sensitisation to *Malassezia* compared to normal individuals (See section on 'Interaction of *Malassezia* with the host immune system'). Studies to determine which species of *Malassezia* might be involved in

**Table 4** Summary of the different *Malassezia* species isolated from lesional skin of diseases, reported in different countries (% patients colonized with each species)

| Country | Disease | *M. globosa* | *M. globosa+other species* | *M. sym* | *M. restricta* | *M. furfur* | *M. slooffiae* | Other species | Negative culture |
|---|---|---|---|---|---|---|---|---|---|
| Spain [62] | PV | **58.2** | 31.7 | 10.1 | | | | | |
| Spain [168] | | **55** | 32 | 11 | 2 | | | | |
| Spain [61] | | **60.4** | 36.5 | 3.1 | | | | | |
| Greece [169] | | **77** | 13 | | | | | 10 | |
| Tunisia [165] | | **47** | 13 | 4 | | 10 | | | 13 |
| Panama [170] | | 5.3 | | 4.6 | | **42** | 5.3 | 0.6 | |
| Mexico [171] | | **47** | | 27 | 13 | 13 | | | |
| India [172] | | **54** | 9.2 | | | 30 | | | |
| Canada [63] | | 25.2 | | **59.4** | | 10.8 | | | |
| Canada [70] | | 17.6 | | **62.7** | | 7.8 | 7.8 | 3.9 | |
| Japan [52] | | **93.9** | | 34.6 | **93.9** | 10.2 | 4.1 | 46.8 | |
| Japan [93] | | **55** | | 9 | | 5 | 5 | | 14 |
| Iran [167] | | **53.3** | | 9.3 | | 25.3 | 4 | 8.1 | |
| Greece [169] | SD | **39** | 18 | | | | | 42 | |
| Spain [69] | | 34 | | 19 | **43** | | | | |
| Canada [70] | | **45** | | 37.5 | | 7.5 | 10 | | |
| Korea [72] | | 60 | | **75** | | | | | |
| Japan [93] | | **21** | | 6 | | **21** | | | 31 |
| Sweden [94] | | 8 | | **33** | 0 | 8 | 17 | 30 | 25 |
| Holland [53] | Dandruff | 41 | | 7 | **64** | 0 | 3 | | 20 |
| Sweden [173] | AD | 23 | | **40** | 2 | 4 | 6 | 25 | |
| Japan [92] | | **75.9** | | 31 | 74.1 | 31 | 3.4 | | |
| Sweden [94] | | **40** | | 31 | 3 | 0 | 11 | 17 | |

The figures for the predominant species are highlighted in bold for each study.

AEDS have yielded divergent results, with *M. globosa, M. restricta* [92], *M. sympodialis* [70,71], and *M. furfur* [93] all found as the predominant species in different studies (see Table 4). The population densities of *Malassezia* on lesional AEDS skin are decreased compared to non lesional AEDS or normal skin [94] and this is likely to be due to the lower skin lipid content in patients with AEDS [95], which will reduce the amount of lipid to support the growth of *Malassezia* species.

*Malassezia* species have also been implicated in a range of other cutaneous diseases, including acne [96], confluent and reticulated papillomatosis [97], psoriasis [98], nodular hair infections [99], onychomycosis [100] and seborrhoeic blepharitis [101]. However, the evidence linking *Malassezia* to these conditions is circumstantial, so a definite causal relationship cannot be assumed.

As well as causing superficial disease, *Malassezia* species are also the causative agents of several deep-seated and systemic infections which have generally occurred in patients with underlying disease or predisposing factors. Mastitis [102], sinusitis [103], septic arthritis [104], malignant otitis externa [105], abscesses [106] and peritonitis in continuous ambulatory peritoneal dialysis patients [107–110] have all been reported. The most widely reported systemic infection, however, is catheter-related fungaemia in premature neonates. First reported in 1981 [111], there are now over 100 cases in the literature both in neonates and adults, usually associated with the administration of total parenteral nutrition through central venous catheters. *Malassezia* colonises the catheter, becoming embedded in a biofilm that seeds organisms into the blood, from where it gains access to the organs, including the lungs and brain resulting in pulmonary vasculitis [111] or meningitis [112]. Removal of the catheter is often the only intervention required to treat fungaemia [113]. Many molecular studies have examined the strains recovered from patients with fungaemia to determine the source of the infection. In some studies strains of *M. pachydermatis* have been transmitted on the hands of health care workers from their animals [114,115], but in other studies no obvious source has been found [116,117].

For several of these unusual infections, the isolation of *Malassezia* and hence the diagnosis may be complicated by the organism's lipid dependent nature as most routinely used mycological media do not support its growth. Use of lipid supplemented media may be warranted in certain specimens, especially if cultures appear 'sterile' on routine media and yeasts have been observed on microscopy. The patient group in whom this may be most appropriate are neonates receiving intravenous nutrition containing high concentrations of lipids when delivered through central venous lines. Supplementation of blood culture bottles with palmitic acid has been shown to improve recovery of *Malassezia* in this patient group [118]. It has been suggested that there is an association with a specific genotypic subgroup of *M. furfur* and systemic disease in humans, however this initial study included limited numbers of isolates and needs to be substantiated by larger studies [45].

## *Malassezia*-associated disease in animals

In addition to causing disease in humans, *Malassezia* species are the causative agents of several diseases in animals (reviewed in [119,120]). *Malassezia d*ermatitis in dogs has been widely studied and presents as pruritic, erythematous lesions, resembling those of AEDS in humans, and usually affecting the abdomen [119]. The condition has been shown to respond to antifungal therapy, suggesting that the yeasts present on the skin of dogs may be involved in the disease. Otitis externa in dogs has also been associated with *Malassezia*, particularly *M. pachydermatis*. In both dermatitis and otitis, dogs affected often have atopic tendencies, which may be significant in the development of these conditions. Infections have also been reported in cats, ferrets, pigs, sea lions, horses, bears and the Indian rhinoceros [119].

## Susceptibility of *Malassezia* species to antifungals

Cutaneous diseases associated with *Malassezia* are usually treated topically with antifungals, although in cases of extensive disease, systemic antifungal therapy may be required. Many antifungals have been used in a variety of regimens and there are also many studies of the *in vitro* susceptibility patterns of the different species, which are summarized in Table 5. Albaconazole and ketoconazole have very good *in vitro* activity against all species tested, and itraconazole also has generally good activity. All the species tested to date are resistant to flucytosine and for other agents the activity varies with the species and sometimes between different isolates of the same species.

Whatever regimen is used, the problem of recurrence is common in patients with pityriasis versicolor, seborrhoeic dermatitis and AEDS. Recurrence occurs because *Malassezia* is present on the skin as a commensal and so removal even with extensive antifungal therapy

**Table 5** *In vitro* activity of compounds against species of *Malassezia*. Range of MICs reported ($n$ = number of tests)*

| Compound | *M. furfur* | *M. sympodialis*[1] | *M. globosa*[2] | *M. restricta*[3] | *M. slooffiae* | |
|---|---|---|---|---|---|---|
| Ketoconazole | ≤0.03–1 (119) | 0.008–0.313 (99) | 0.008–0.125 (70) | 0.016–0.626 (31) | 0.008–0.06 (41) | |
| Fluconazole | 2–32 (24) | 0.25–16 (21) | 12.5–50 (27) | 0.5–1 (2) | 1–4 (19) | |
| Clotrimazole | ND | 1–2 (2) | 0.0125–12.5 (21) | 1–2 (2) | ND | |
| Itraconazole | ≤0.03–25 (123) | 0.016–0.2 (95) | 0.016–6.3 (92) | 0.0156–6.3 (32) | 0.016–0.8 (46) | |
| Miconazole | 4–128 (22) | 0.12–4 (44) | 0.05–50 (26) | 1–2 (2) | 2–4 (3) | |
| Econazole | 4–128 (22) | 0.12–4 (42) | 0.05–12.5 (24) | ND | 0.25–0.5 (3) | |
| Bifonazole | 6.3–50 (26) | 0.1–1.6 (14) | 0.8–6.3 (1*) | 0.1–0.8 (1*) | 0.1–6.3 (4) | |
| Albaconazole | ≤0.06 (24) | ≤0.06 (21) | ND | ND | ≤0.06 (15) | |
| Voriconazole | ≤0.03–16 (85) | ≤0.03–0.125 (31) | ≤0.03–0.12 (29) | ≤0.03 (6) | ≤0.03–0.25 (22) | |
| Posaconazole | 0.03–32 (12) | 0.03–0.06 (8) | 0.03–0.06 (22) | 0.03 (2) | 0.03 (4) | |
| Terbinafine | ≤0.03–50 (46) | ≤0.03–6.3 (42) | 0.06–16 (40) | 0.06–4 (17) | ≤0.03–25 (11) | |
| Amorolfine | 3.2–50 (26) | 0.2–12.5 (14) | 3.2–6.3 (1*) | 6.3–25 (1*) | 0.8–50 (4) | |
| Flucytosine | >64 (24) | >64 (21) | ND | ND | >64 (15) | |
| Amphotericin B | 0.12–16 (12) | 0.06–0.5 (8) | 0.10–4 (22) | 4–8 (2) | 0.5–8 (4) | |
| Tacrolimus | 16– >32 (12) | 16– >32 (24) | 16– >32 (27) | 16– >32 (23) | 16– >32 (12) | |
| Compound | *M. obtusa* | *M. dermatis* | *M. nana* | *M. japonica* | *M. yamotoensis* | *M. pachydermatis* |
| Ketoconazole | 0.008–0.06 (16) | 0.016–0.25 (5) | 0.016 (4) | 0.016 (2) | 0.016 (2) | 0.001–0.06 (24) |
| Fluconazole | 2 (2) | 2 (2) | ND | ND | ND | 4–16 (11) |
| Clotrimazole | ND | ND | ND | ND | ND | ND |
| Itraconazole | 0.016–1.6 (20) | 0.016–0.03 (5) | 0.016 (4) | 0.016 (2) | 0.016 (2) | 0.016–6.3 (45) |
| Miconazole | 0.5–2 (2) | ND | ND | ND | ND | ND |
| Econazole | 0.5–4 (2) | ND | ND | ND | ND | ND |
| Bifonazole | 0.1–3.2 (6) | ND | ND | ND | ND | 3.2–25 (24) |
| Albaconazole | ND | ND | ND | ND | ND | ≤0.06 (10) |
| Voriconazole | ≤0.03–0.06 (5) | 0.12 (2) | ND | ND | ND | ≤0.03–0.25 (15) |
| Posaconazole | 0.03 (2) | 0.03–0.5 (2) | ND | ND | ND | 0.12 (1) |
| Terbinafine | 0.03–64 (11) | 0.03–4 (2) | ND | ND | ND | ≤0.03–50 (29) |
| Amorolfine | 3.2–12.5 (6) | ND | ND | ND | ND | 3.2–50 (24) |
| Flucytosine | ND | ND | ND | ND | ND | >64 (10) |
| Amphotericin B | 0.03–0.06 (2) | 0.03–0.12 (2) | ND | ND | ND | 0.12 (1) |
| Tacrolimus | 16– >32 (9) | ≥32 (3) | ≥32 (4) | 32 (2) | >32 (2) | ≥32 (6) |

*Data compiled from refs [174–185]. ND = No data. (1*) = Replicate results from testing a single isolate.
[1]Including isolates originally described as *M. furfur* serovar A.
[2]Including isolates originally described as *P. orbiculare* or *M. furfur* serovar B.
[3]Including isolates originally described as *M. furfur* serovar C.

is not a realistic aim and patients should be warned of the relapsing nature of these conditions.

In catheter-related fungaemia, removal of the catheter and discontinuation of the parenteral lipid is often sufficient without antifungal therapy, but amphotericin B or fluconazole have been used, although some fluconazole resistance isolates have been reported [113]. *Malassezia* species appear to be resistant to flucytosine, at least *in vitro* so this agent should not be used.

## Interaction of *Malassezia* with the host immune system

The way in which *Malassezia* interacts with the host immune system is, in many ways, paradoxical. It has the ability to stimulate the immune system via the classical [121] and alternative [122,123] complement pathways, it acts as an adjuvant [124,125] and elicits both humoral [126] and cellular [127] immune responses in healthy individuals and also individuals with conditions associated with *Malassezia* species. In contrast, it is able to resist phagocytic killing by neutrophils [128] and downregulate cytokine responses when co-cultured with peripheral blood mononuclear cells (PBMC) [129]. These apparently contradictory behaviours may be related to the lipid-rich capsular-like layer that surrounds the yeast cells [9]. Removal of the capsular-like layer reverses the suppression of cytokine production by PBMC [130], however, it is of more relevance to determine whether the same effect occurs when *Malassezia* is co-cultured with keratinocytes. In

ongoing work, Thomas *et al*. have examined the effect of *Malassezia* species, with and without the capsular-like layer and their effects on cytokine production when co-cultured with normal human keratinocytes [131]. Co-culture of capsulated yeasts of all species with keratinocytes resulted in limited IL-1 α, IL-6 and TNFα production, suggesting that the presence of the capsule suppressed pro-inflammatory cytokine release and prevents an inflammatory response. The effects of decapsulated yeasts varied with the species of *Malassezia*; decapsulated *M. globosa* and *M. slooffiae* caused significantly increased ($p < 0.05$) release of IL1α; decapsulated *M. furfur, M. obtusa, M. restricta* and *M. sympodialis* significantly increased ($p < 0.05$) release of IL6; and all the species tested (*M. furfur, M. globosa, M. obtusa, M. restricta, M. slooffiae, M. sympodialis*) caused a significant increase in the release ($p < 0.05$) of IL8 [132]. Thomas *et al*. suggested that if there were local variations in the lipid available on the skin to be incorporated into the capsule, this might result in thinning or absence of the capsule and a concomitant increase in the inflammatory response seen. Patients with AEDS have a lower lipid skin content than healthy individuals [95] and under these conditions, it is likely that *Malassezia* yeasts present on lesions will have a thinner or absent capsule with a resultant increase in the inflammatory potential of the organism.

The interaction of *Malassezia* with keratinocytes and dendritic cells has recently been reviewed [133] and will not be covered in more detail here.

The exact role that *Malassezia* plays in the immunopathogenesis of AEDS has been studied intensively over the last 10 years and our understanding of this has advanced markedly. Patients with AEDS have significantly more sensitisation to *Malassezia* than healthy controls as demonstrated by (i) increased type I hypersensitivity to *Malassezia* [134]; (ii) increased prevalence of *Malassezia*-specific IgE [135,136]; (iii) *Malassezia*-specific $Th_2$ response [137]; and, (iv) induction of eczematous lesions after contact with *Malassezia* [138]. Kosonen *et al*. [139] have demonstrated that in AEDS patients there is a correlation between the *in vitro* measurement of *Malassezia*-specific IgE and the *in vivo* measurement using skin prick tests, however, neither of these correlated with the severity of disease or outcome with antifungal therapy. It has been postulated that AEDS patients may develop autoreactivity to human proteins and that the antigens which initiate this autoreactivity are microbial antigens that exhibit molecular mimicry. Two antigens described in *M. sympodialis*, designated Mala s 6 and Mala s 11, show significant sequence homology to human proteins, namely cyclophilins and manganese superoxide dismutase (MnSOD) [140–142]. Patients with reactivity to human MnSOD have been shown to have cross-reactivity to an extract from *M. sympodialis*, which was thought to contain Mala s 11, so this antigen from *Malassezia* may trigger reactivity to human MnSOD by a process of molecular mimicry and so contribute to the exacerbation of lesions in AEDS [143]. Another line of evidence indicating a role for *Malassezia* in AEDS is the finding that atopy patch testing with *Malassezia* extracts elicits eczematous reactions, with a predominantly $Th_2$-type cytokine response [144,145]. In a recent large study of 97 patients with AEDS and 571 patients with other forms of allergic reaction or atopy, *M. sympodialis* specific IgE reactions were found almost exclusively in the AEDS patients [146]. The study used *M. sympodialis* specific IgE to the ImmunoCap m70 antigen, atopy patch tests, skin prick tests and lymphocyte transformation assays and found positive reactivity in the tests only occurred in patients with either extrinsic or intrinsic atopic eczema, prompting the authors to suggest that these tests should be used as part of the diagnostic workup for these conditions. IgE to the m70 antigen is more commonly positive in adults in whom the AEDS is ongoing, compared with adults in whom the disease is resolved [147]. Other antigens present in *M. sympodialis* are also recognized by the immune system and are thought to be important in AEDS, and although one has been crystallized, Mala s 1, its function is as yet unknown [148]. The skin of patients with AEDS has a slightly higher pH than normal skin and when grown under similar conditions *in vitro M. sympodialis* produced and released more antigens, which may exacerbate the inflammation these antigens elicit [149] if similar effects occur *in vitro*.

Antimicrobial peptides are important components of the non-specific immune system and several are present in human skin, including β-defensins, LL37 (a cathelicidin), dermcidin and psoriasin [150]. LL37, magainin, PR-39 and cecropin P1 have been shown to have activity against *Malassezia* yeasts, with MICs in the range 20–30 μM [151]. LL37 expression is upregulated in keratinocytes that are cultured in the presence of *Malassezia* cells and *in vivo* in patients with pityriasis versicolor, LL37 expression is also increased, suggesting that this peptide is involved in the host response against the yeast. In patients with AEDS, levels of LL37 and β-defensins are deficient in the lesions [152], however, when monocyte derived dendritic cells from patients with severe AEDS are co-cultured with *M. sympodialis*, higher levels of LL37 were induced compared to less severe AEDS or normal individuals [153]. This suggests that in normal healthy skin production of LL37 is limited, allowing *Malassezia* to

exist as a commensal. However, some upregulation occurs in pityriasis versicolor, in an attempt to eradicate the yeast, but in AEDS levels become so high that they lead to detrimental effects and sustained inflammation in the lesions.

Toll-like receptors (TLR) are a family of proteins involved in microbial recognition during non-specific immune responses via pathogen-associated molecular patterns (PAMPs) [154]. TLR2 and 4 are involved in recognition of *C. albicans* and *A. fumigatus* and activation of TLR's can lead to release of β-defensins. Co-culture of normal human keratinocytes with *M. furfur* increases gene expression of TLR2, MyD88 (a protein of the signalling pathway triggered by TLR2), human β defensin 2 (HBD2) and IL8 and the induction of IL8 and HBD2 is dependent on TLR2 [155]. Thus, this is one mechanism by which *Malassezia* can induce inflammation via the innate immune system in the skin.

In conclusion, it is now apparent that although the genus *Malassezia* currently contains 11 species, genetic variation within some species may lead to the description of new species as further molecular studies are performed. Recent work on the interaction of *Malassezia* spp. and the host, especially in AEDS, demonstrate that far from being an 'innocent bystander' the organisms play a significant role in the initiation and maintenance of inflammation in several cutaneous diseases. The distribution of species on normal skin and in disease shows significant variation and currently the evidence is not conclusive that any given species is responsible for a specific disease. Rather, the situation is complex with particular host predispositions and yeast properties interacting dynamically to result in disease. As our understanding of these interactions increase, it may allow us to control or even prevent these diseases in the future.

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