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The Malassezia Genus in Skin and Systemic Diseases

Georgios Gaitanis, Prokopios Magiatis, Markus Hantschke, Ioannis D. Bassukas and Aristea Velegraki
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The *Malassezia* Genus in Skin and Systemic Diseases

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INTRODUCTION

Malassezia yeasts are unique under the view that they comprise almost exclusively the single eukaryotic member of the microbial flora of the skin. However, the complexity of the interaction of a unicellular eukaryotic organism (*Malassezia*) with a tissue of a multicellular organism (skin) makes understanding the

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interactions and development of disease a complex process. This is easily understood by the fact that once a revision of the genus *Malassezia* was described in a seminal publication by Guého et al. in 1996 (129), in addition to studying the epidemiology of this yeast in healthy and diseased skin, the need to repeat the already inconclusive experiments in relation to *Malassezia* immunology surfaced (14). Furthermore, the expansion of our knowledge on the complex homeostatic mechanisms of the skin increases the candidate targets of interactions between this yeast and skin cells.

In this article, in addition to reviewing the taxonomy and identification methods for the currently accepted *Malassezia* species, an effort is also made to critically assess the available data on *Malassezia* epidemiology and nosology in humans and the existence of pathogenic subtypes within *Malassezia* species, their biological characteristics, and their relevance to skin disease. Therapeutic approaches for the treatment of pityriasis versicolor, the prototypical *Malassezia*-associated skin disease, will be briefly discussed. Furthermore, data on *Malassezia* systemic infections are reviewed, and provisional diagnostic criteria are proposed.

TAXONOMY AND IDENTIFICATION METHODS

An overview of the historical events underlying *Malassezia* taxonomy may be considered *prima facie* avoidable in the era of metagenomics. To reduce biased interpretations of taxonomic issues, it was deemed essential to refer to the succession of scientific inquiries that in the last 20 years brought about scrupulous research on diverse domains covering *Malassezia* biology. In many respects, the series of events preceding the current taxonomic status account for the numerous, independently derived theories regarding the role of *Malassezia* as a skin commensal and pathogen.

Current taxonomy places *Malassezia* (Baillon) yeasts (19) in the Phylum *Basidiomycota*, subphylum *Ustilaginomycotina*, class *Exobasidiomycetes*, order *Malasseziales*, and family *Malasseziaceae*. Today, the genus *Malassezia* includes 14 lipophilic species that have been isolated from healthy and diseased human and animal skin. However, *Malassezia* yeasts have been recognized for more than 150 years (91) as members of the human cutaneous flora and etiologic agents of certain skin diseases. As early as the early 1800s, it was noted that yeast cells and filaments were present in the skin scales of patients with pityriasis versicolor (267), whereas yeast cells, but no filaments, were observed in scales from healthy scalp, seborrheic dermatitis scalp, and dandruff. The absence of filaments in seborrheic dermatitis and dandruff lesional scales for many years led to uncertainty regarding the placement of yeast isolates from pityriasis versicolor and those from seborrheic dermatitis and dandruff into the same genus (32, 208, 274). Eventually, Sabouraud (274) placed them into separate genera and named the yeasts forming filaments in pityriasis versicolor skin scales *Malassezia furfur* and those which did not form filaments in dandruff and seborrheic dermatitis skin scales *Pityrosporum malassezii*. Almost a decade later, *Pityrosporum malassezii* was allotted the binomial nomenclature *Pityrosporum ovale* by Castellani and Chalmers (50) Subsequently, the lipid dependence of the growth of these yeasts was established (127), and it was confirmed that *Pityrosporum orbiculare* and *P. ovale* are variants of the same species (97).

From a historical standpoint, it is interesting that isolates from exfoliative dermatitis of a rhinoceros described by Weidman in 1925 (332) and from otitis externa of dogs described by Gustafsson in 1955 (139), although given the names *Pityrosporum pachydermatis* and *Pityrosporum canis*, respectively, were in due course found to have similar morphologies. As both isolates did not require lipid supplements for growth in culture, *P. canis* was accepted as a synonym for *P. pachydermatis*. Therefore, since 1970, and for approximately 14 years, it was acknowledged that the genus *Pityrosporum* included three species: *P. ovale*, *P. orbiculare*, and *P. pachydermatis* (292). During that time, the morphological similarities between *Pityrosporum* and *Malassezia*, as described by Eichstedt (91) and by Panja (240), were assessed. Hence, in the early 1980s, a reevaluation of those previous studies instigated among taxonomists an unequivocal acceptance of the genus name *Malassezia* over that of the genus name *Pityrosporum*. This was based on the morphology, ultrastructure (25, 246), and immunological properties (293, 310) of *Malassezia* yeasts. In addition, (i) microscopic observations of hyphae in skin scales from pityriasis versicolor lesions and (ii) confirmation of hyphal production by *P. orbiculare* clinical isolates in culture (87, 233) confirmed its placement in the genus *Malassezia*. Hence, within the genus *Malassezia*, the species *M. furfur* integrated both lipid-dependent yeasts, formerly referred to as *P. orbiculare* and *P. ovale* (342). However, toward the end of the 1980s, further studies demonstrated the existence of several *M. furfur* serovars (69, 221), providing evidence of diversity within the genus, which was observed *in vivo* as well as *in vitro*. Following pioneering work based on studies of nuclear DNA G+C content and a DNA-DNA hybridization technique, a new species, *Malassezia sympodialis*, was defined (290). Eventually, the genus *Malassezia* was revised and enlarged in 1996 to include 7 species (129). In a description of the new species by Guého et al. (129), conventional and modern spectrum techniques were employed, encompassing morphology, ultrastructure, physiology, and molecular biology. As a result, the genus included seven species, the three former taxa *M. furfur*, *M. pachydermatis*, and *M. sympodialis* and four new taxa, *M. globosa*, *M. obtusa*, *M. restricta*, and *M. slooffiae*. Lipid dependence for growth remained a common feature among all species, with the exception of *M. pachydermatis*, and molecular data were in accordance with phenotypic properties, which differed among species. These properties included differential per-species abilities to utilize lipid supplements, catalase and beta-glucosidase reactions, and temperature tolerance at 32°C, 37°C, and 40°C, thus providing a phenotypic identification algorithm for the routine identification of *Malassezia* isolates to the species level (Table 1). Despite the undisputable value of phenotypic identification, ambiguous results have been reported (132). For example, an accurate differentiation among *M. furfur*, *M. sympodialis*, and *M. slooffiae* isolates is often hindered because results from physiological tests on the basis of Tween compound utilization are very similar (Table 1).

Undoubtedly, since the mid-1990s, molecular techniques, and in particular rRNA sequencing analysis (131), advanced *Malassezia* systematics, linked molecular systematics to the circumscription of new species, and warranted nonculture detection and identification of *Malassezia* species in patient skin scales from a variety of *Malassezia*-associated or -exacerbated diseases (114, 119, 295). This also accelerated developments in PCR-based identification methods (Table 2), promoted investigation into *Malassezia* epidemiology (64, 112) and pathobiology (108), and encouraged re-

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TABLE 1 Routine phenotypic characterization of 14 *Malassezia* species based on their identifiable physiological and biochemical properties[a]

Malassezia species	Presence of growth on:				Test result							Reference
	SDA at 32°C	mDA			Tween utilization				Cremophor EL utilization	β-Glucosidase	Catalase	
		32°C	37°C	40°C	Tween 20	Tween 40	Tween 60	Tween 80				
M. furfur	−	+	+	+	+/IGP	+/IGP	+/IGP	+/IGP	+/− IGP	+/− IGP	+/− IGP	129
M. sympodialis	−	+	+	+	−/±	+	+	+	−/±	+	+	129
M. globosa	−	+	−/±	−	−	−/IGP	−/IGP	−	−	−	+	129
M. restricta	−	+	v	−	−	−/IGP	−/IGP	−	−	−	−	129
M. obtusa	−	+	−/±	−	−	−	−	−	−	+	+	129
M. slooffiae	−	+	+	+	+/±	+	+	−/±	−	−	+	129
M. dermatis	−	+	+	+	+	+	+	+/±	+/±	NE	+	288
M. japonica	−	+	+	−	−	±	+	−	NE	NE	+	287
M. nana	−	+	+	v	v	+	+	±	−	−	+	147
M. yamatoensis	−	+	+	−	+	+	+	+	NE	NE	+	285
M. equina	−	+	±	−	±	+	+/IGP	+/IGP	−	−	+	38
M. caprae	−	+	−/±	−	−/IGP	+/IGP	+/IGP	+/− IGP	−	+/− IGP	+	38
M. cuniculi	−	+/±	+	+	−	−	−	−	−	+	+	39
M. pachydermatis	+/±	+	+	+	+/IGP	+	+	+	+/IGP	+/− IGP	+/±	129

[a] SDA, Sabouraud dextrose agar (also referred to as glucose peptone agar [GPA] by several authors; mDA, modified Dixon's agar; SDA, Dixon's agar supplemented with water-soluble lipids, such as Tweens and Cremophor EL, to identify lipophilic and lipid-dependent *Malassezia* species; ±, weak growth; v, variable; IGP, inconsistent growth pattern (rarely observed); NE, not evaluated (in the description of this species).

search on the association of certain *Malassezia* species with specific geographical locations (136).

In addition, molecular systematics had an impact on the recognition of new *Malassezia* species associated with human and animal disease. By 2004, three more new species were described: *Malassezia dermatis* and *M. japonica*, isolated from Japanese atopic dermatitis (synonym, atopic eczema) patients (299, 300), followed by *M. yamatoensis*, isolated from healthy human skin and from a patient with seborrheic dermatitis (297). New lipid-dependent species, such as *M. nana* (150), *M. caprae*, *M. equina* (39), and, recently, *M. cuniculi* (40), from animal skin were also described, raising the number of currently recognized *Malassezia* species to 14.

EPIDEMIOLOGY

Culture-Based Epidemiology

More than 20 studies (Tables 3 to 6) have been carried out worldwide on the epidemiology of *Malassezia* species in cases of pityriasis versicolor, seborrheic dermatitis, atopic eczema, and psoriasis and on healthy control skin of the same individuals or skin from healthy volunteers (53, 63, 89, 112, 122, 146, 171, 173, 180, 185, 228, 237, 255, 259, 275, 286, 344, 353). Results are not directly comparable between studies, as different methodologies, isolation media, and identification procedures have been employed. However, these results can be used for the extraction of interesting conclusions on the epidemiology and pathobiology of *Malassezia* species. Furthermore, it should be noted that in all those studies, the surface of the skin was sampled and not the hair infundibulum, which is the niche of *Malassezia* yeasts. From the available data (Tables 3 to 6), we can conclude that the 7 *Malassezia* species described in 1996 (68) are the most common ones, while geographical variations in species distribution are apparent. *M. dermatis* has been isolated in East Asia (Japan and South Korea), while *M. obtusa* has been isolated mostly in Sweden, Canada, Bosnia, and Herzegovina but has also been reported in Iran and Indonesia. Identification and typing of the latter isolates with molecular techniques might reveal the existence of atypical *M. obtusa*-*M. furfur* subtypes, as these two species are phylogenetically close, and *M. furfur* shows considerable diversity (106, 315).

Non-Culture-Based Epidemiology

Interesting results have been obtained from studies of *Malassezia* population dynamics in healthy or diseased human skin employing techniques that directly identify and quantify *Malassezia* DNA from skin specimens (Table 7). No substantial difference was found in the distributions of *Malassezia* species subtypes identified in the left and right halves of the body skin of healthy volun-

TABLE 2 Identification of *Malassezia* species from pure culture by sequencing and/or PCR-based methods[a]

PCR-based method and genomic region	Origin(s) of strains and *Malassezia* species	Reference(s)
ITS amplification and sequencing	Culture collection strain of *M. furfur*; clinical isolates of *M. pachydermatis*, *M. restricta*, *M. dermatis*, *M. caprae*, *M. equina*, *M. cuniculi*	39, 40, 194, 256, 257, 303
ITS amplification, REA, and sequencing and ITS and REA only	Type, neotype, culture collection strains, and clinical isolates of *M. furfur*, *M. obtusa*, *M. globosa*, *M. slooffiae*, *M. sympodialis*, *M. restricta*, *M. pachydermatis*, *M. dermatis*, *M. japonica*, *M. nana*, *M. yamatoensis*	111, 114, 286
26S rRNA gene (LSU) amplification and REA and 26S rRNA gene (LSU) amplification and sequencing	Clinical isolates of *M. furfur*, *M. obtusa*, *M. globosa*, *M. slooffiae*, *M. sympodialis*, *M. restricta*, *M. pachydermatis*, *M. dermatis*, *M. caprae*, *M. equina*, *M. cuniculi M. japonica*, *M. nana*, *M. yamatoensis*	39, 40, 47, 130, 137, 164, 223, 238
DNA microcoding array (Luminex xMAP platform)	*M. furfur*, *M. obtusa*, *M. globosa*, *M. slooffiae*, *M. sympodialis*, *M. restricta*, *M. pachydermatis*, *M. dermatis*, *M. japonica*, *M. nana*, *M. yamatoensis*, *M. equina*	82

[a] ITS, internal transcribed spacer (ITS1-5.8S-ITS2) of the ribosomal DNA region; REA, restriction enzyme analysis; LSU, large subunit.

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TABLE 3 Results from culture-based epidemiological studies of healthy skin

Reference	No. of patients/ no. of positive cultures	% of cultures positive for:							Culture medium[a]	Location(s)	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*			
353	123/107	78	1	7	21				LNA	Iran	7% mixed species (>2 species isolated); percentages correspond to avg of 3 samplings/patient
238	60/38	28	32	29	5	1	1	4	LNA	South Korea	Variations in isolation of species according to age; variation, yet not significant, in isolation of species according to body part; *M. restricta* on the forehead, *M. sympodialis* and *M. globosa* on the chest
164	160/599 (960 samples)	22	22	12	4.5	2	0.5	2	LNA	South Korea	*M. globosa* and *M. restricta* were found more commonly in different age groups; *M. restricta* and *M. globosa* were found more commonly on the scalp; *M. globosa* and *M. sympodialis* were found more commonly on the trunk; mixed species were commonly isolated
254	40/32	40		20	17.5	2.5			mDA	Bosnia and Herzegovina	Healthy trunk skin of seborrheic dermatitis patients
255	90/82	49		37	5.5				mDA	Bosnia and Herzegovina	Healthy trunk skin of pityriasis versicolor patients, away from lesions; no association of the isolated species with sex, age, clinical appearance of pityriasis versicolor (hyper- or hypopigmented), duration of disease
135	245/172	32	1	57	6	3			LNA	Canada	Differences in isolation rates of species between age groups and body locations were recorded; no mixed species isolated
138	20/19	28	6	47	11	7.5			LNA	Canada	CFU was equivalent to that associated with pityriasis versicolor and significantly more than those for psoriasis, seborrheic dermatitis, and atopic eczema
195	120 (600 samplings)/393	41	49	6	4	2			LNA	South Korea	*M. restricta* was more common on the forehead and in younger age groups (<50 yr old); *M. globosa* was more frequent in patients aged >50 yr
311	100/60	42	3	25	23	7			DA	Iran	
277	31/26	12		69		4	15		LNA	Sweden	Mixed species were cultured in 11% of patients; healthy skin and seborrheic dermatitis skin were significantly more colonized than atopic eczema skin
228	105/52	42	2	21	6	2			DA	Japan	Two groups of healthy volunteers, i.e., 35 random volunteers and 73 medical school students; *M. globosa*, *M. furfur*, and *M. sympodialis* were isolated more frequently from scalp and face, but there was a low recovery rate for both groups studied; *M. globosa* and *M. sympodialis* were isolated from the trunks of healthy volunteers
275	35/11	49	8	23	20.5	2			mDA	Tunis	3 sampling sites per patient, more than 1 isolate per patient; frequency of *M. globosa* on pityriasis versicolor skin was significantly higher than that on healthy skin

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TABLE 3 (Continued)

Reference	No. of patients/ no. of positive cultures	% of cultures positive for:							Culture medium[a]	Location(s)	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*			
171	58/37		19			50			CHROMagar *Malassezia*	Japan	Sampling of the external ear canal was performed; *M. slooffiae* was characterized as a specific isolate with increasing prevalence after the age of 30 yr

[a] NA, Leeming-Notman agar; mDA, modified Dixon's agar; DA, Dixon's agar.

teers and psoriasis patients (243, 244). Also, there was no significant difference in the ribosomal DNA (rDNA) sequences of the strains colonizing healthy and psoriasis skin (243, 244). The predominant species in non-culture-based epidemiological studies are *M. globosa* and *M. restricta*, which are found on the skin of practically all humans. However, this introduces ambiguity regarding their pathogenic potential, as they are found on healthy and diseased skin equally, thus not fulfilling Koch's postulates. For this reason, the use of robust typing methods, such as multilocus sequencing typing, for the screening of pathogenic versus nonpathogenic *Malassezia* strains would highlight the pathobiology of *Malassezia* yeasts.

Molecular typing of *Malassezia* yeasts. Current data (Table 8) point toward the existence of pathogenic subtypes of *M. furfur* (113, 170, 350), *M. globosa* (112, 307), and *M. restricta* (296, 307). The *Malassezia* microbiota was suggested to be host specific (243). Moreover, for *M. furfur*, phylogeographic associations have also been found in Greek, Swedish, and Bulgarian strains (106) as well as in the Han and Tibetan ethnic groups in China (350). *M. sympodialis* seems to represent a homogenous species, with no pathogenic subtypes detected by current molecular methods. However, our current molecular typing approaches are limited, as they provide only indirect evidence on virulence. In that respect, neither the observed sequence variation within the rDNA complex nor the polymorphism determined by PCR-based methods (Table 8) accounts for actual virulence. Essentially, these methods depict disease-associated subtypes that could represent pathogenic lineages whose survival is favored on diseased skin under conditions which are presently inadequately understood.

Conclusion

In the ongoing debate on the usefulness of conventional epidemiological studies on the distribution of *Malassezia* species, it should be noted that more accurate epidemiological data on species distribution can be acquired by non-culture-based molecular techniques. However, conventional culture and identification methods offer the advantage of further evaluating the isolates for possible virulence factors, such as the production of phospholipase (44, 170) and indole (108, 184, 336) and melanin synthesis (107). Furthermore, this was highlighted in a study by Akaza et al. (6), in which the seasonal rates of isolation of *Malassezia* species from healthy skin determined by quantitative PCR (qPCR) were compared with those determined by use of Leeming-Notman agar (197). Increased *Malassezia* colonization of the skin in summer was determined by culture but not by PCR. This finding can be attributed to the ability of culture to select viable cells, while PCR also quantifies DNA from nonviable or not metabolically active cells. Furthermore, the initial optimism on the pathogenic potential of *M. globosa* and its characterization as the causative agent of pityriasis versicolor (63) was subsequently weakened by findings supporting the widespread distribution of this species on healthy skin as well as in seborrheic dermatitis, atopic eczema, and psoriasis skin lesions (Tables 3 to 6). The matter is further complicated by the lower rate of recovery of *Malassezia* yeasts from lesional skin in the latter three skin diseases than from healthy skin, which points toward the existence of metagenomic alterations in the pathogenic strains of *Malassezia* species in order to survive in the altered environment of diseased skin.

MALASSEZIA INTERACTION WITH EPIDERMAL AND IMMUNE CELLS

Gradually, experimental data on the multiple facets of the interaction of *Malassezia* yeasts with different cell types are being collected. Although safe conclusions cannot be drawn, this area of research remains a promising field.

Experimental Data

Malassezia yeasts demonstrate a species-specific ability to interact with cells that are constitutive members of the skin and its adnexal structures, such as various keratinocyte subpopulations, or cell lineages that are involved in immune functions, including antigen-presenting dendritic cells, macrophages, eosinophils, and neutrophils (Table 9). The exposure of the above-mentioned cells to *Malassezia* yeasts or their products has been shown to induce the production of a variety of cytokines; however, the results are not directly comparable, as different cell lines and protocols have been employed (Table 9). The effect of *Malassezia* yeasts on cytokine production from keratinocytes *in vitro* depends on the culture phase of the yeast (stationary versus exponential), on the *Malassezia* species used, and on the previous manipulations (removal or not) of the yeast cell lipid layer (316). However, this does not universally apply to all the immune response-regulating molecular pathways that operate in epidermal keratinocytes, as it was recently shown that *M. globosa* and *M. restricta* could equally efficiently stimulate lysophosphatidic acid receptors in these cells and increase the production of thymic stromal lymphopoietin (160). This property was abrogated when the lipid layer was removed from *Malassezia* cells. Thymic stromal lymphopoietin may participate in the pathogenesis of atopic eczema, as it can promote a Th2 inflammatory response through corresponding dendritic cell activation. Furthermore, *Malassezia* yeasts have the ability to bind C-type lectins, which are a diverse group of proteins that have the ability to recognize carbohydrate structures and, upon ligand binding, induce cellular responses with immune and nonimmune functions (128). In mast cells of atopic eczema patients, the expression of dectin-1 and the response to *M. sympodialis* exposure are modified compared to those of mast cells from healthy individuals (264), and this finding points toward additional host sus-

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TABLE 4 Results from culture-based epidemiological studies of pityriasis versicolor lesions

Reference	No. of patients/no. of positive cultures	% of cultures positive for:								Culture medium[a]	Location(s)	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*	*M. pachydermatis*			
63	96/93	97		33		7				mDA	Spain	*M. sympodialis* and *M. slooffiae* were coisolated with *M. globosa* in 36.5% of patients; no association of *Malassezia* species with clinical form, pityriasis versicolor episode, or severity
138	23/21	18		63	8	8	4			LNA	Canada	CFU from pityriasis versicolor skin was equivalent to that from healthy skin and significantly more than that from psoriasis, seborrheic dermatitis, and atopic eczema skin
136	129	25		59.5	11	4	2			LNA	Canada	1 colony per culture was processed for identification; no species was particularly associated with body site
188	100/87	56.5	2	10	25	1				mDA	Tunis	18 mixed cultures of *M. globosa* with *M. sympodialis* or *M. furfur*
180	70/48	40	2	58						mDA	India	Only direct-microscopy specimens were cultured; no mixed cultures identified
53	90/87	57.5	3	15	1		1			mDA	India	No difference in isolation rates of species in patients ≤20 or >20 yr old as well as between genders
259	166/116	44	9		30	7			10.5	mDA	Iran	Prevalence of *Malassezia* species varied according to age, gender, and anatomic location
286	69/61	48	2	8	41					LNA	Iran (Northern)	No correlation between *Malassezia* species and body site sampled or age
311	94/75	53		9	25	4	8			DA[k]	Iran	No difference in distribution of species between healthy and pityriasis versicolor skin
255	90/90	63		14	10	4	8			mDA	Bosnia and Herzegovina	No mixed cultures observed; upon direct microscopy of pityriasis versicolor scales, evidence of mixed species was found in 37% of isolates; no association of species and clinical appearance of lesions
112	76/71	77	2	13	5	3				mDA	Greece	*M. globosa* was isolated in 90% of cases in association with one of the other species
122	218/239	38	1	37	21	2		0.5		mDA	Argentina	In 15/218 patients, 2 species were coisolated, and in 3/218 patients, 3 species were coisolated; percentages refer to isolates and not patients
89	427/250	64		5	34					mDA	India	23/250 patients had mixed cultures with *M. globosa*
185	98/91	14	1	27.5	34	10	6			LNA	Indonesia	Without reaching statistical significance in the isolation rate, *M. furfur* was not found in patients with duration of disease of <1 mo; no difference in distribution of species and age or gender
173	97/44	48			36	16				mDA	Turkey	Mixed species were not isolated; statistical differences in species distribution and duration of disease, sun-exposed or sun-protected lesions, hypo- or hypepigmented skin

[a] mDA, modified Dixon's agar; LNA, Leeming-Notman agar; DA, Dixon's agar.

ceptibility factors that interact with *Malassezia* cellular components and result in the aggravation of atopic eczema. The activation of the C-type lectin Mincle in murine macrophages, through interactions with *Malassezia* yeasts, led to increases in the induction of tumor necrosis factor alpha (TNF-α), macrophage inflammatory protein 2 (MIP-2), keratinocyte chemoattractant (KC), and interleukin-10 (IL-10) in a yeast/cell-dependent fashion, which was partly reduced in Mincle-deficient cells (340). Although this was originally observed for a strain of *M. pachydermatis*, binding to Mincle was further confirmed for the lipophilic species *M. dermatis*, *M. japonica*, *M. nana*, *M. slooffiae*, *M. sympodialis*, and *M. furfur*. Another C-type lectin, langerin, characteristically found in epidermal antigen-presenting Langerhans cells, was shown to bind extracts of *M. furfur* but not *M. pachydermatis* (79). However, effective binding to both of the latter species was observed when live cells and different *Malassezia* strains were used (312). Earlier studies showed that the uptake of *M. furfur* from human monocytes could be abrogated by coculture with soluble mannan and β-glucan (305), possibly through interactions with those receptors. It is most probable that the induction of cytokines

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TABLE 5 Results from culture-based epidemiological studies of seborrheic dermatitis

Reference	No. of patients/no. of positive cultures	% of cultures positive for:								Culture medium[a]	Location(s)	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*	*M. japonica*			
138	28/23	45		37.5	7.5	10		8		LNA	Canada	Patients in this group had higher CFU counts in healthy than in diseased skin
238	60/31	22.5	38	28	9			3		LNA	South Korea	Variations in isolation of species according to age; variation, yet not significant, in isolation of species according to body part; *M. restricta* on forehead, *M. sympodialis* and *M. globosa* on chest
146	100/77	56	9	1	32.5				1	LNA	Iran	*M. globosa* was more commonly isolated from face, *M. furfur* was more commonly isolated from trunk
277	16/14	36		43	7	14	43			LNA	Sweden	Mixed species were cultured in 11% of patients; healthy skin and seborrheic dermatitis skin were significantly more colonized than atopic eczema skin
112	45/38	58	48	8	2	5				mDA	Greece	Strains of less common species were coisolated with *M. globosa* and *M. restricta*
228	42	21		6	21					DA	Japan	No difference in isolation rate of *M. globosa* and *M. furfur* from lesional and nonlesional skin, but these two species were significantly more common than in skin of healthy subjects
254	40/35	17.5	27.5	12.5	12.5	15				mDA	Bosnia and Herzegovina	2.5% of patients had *M. pachydermatis* on lesional skin; isolation from scalp/face was performed

[a] LNA, Leeming-Notman agar; mDA, modified Dixon's agar; DA, Dixon's agar.

from *Malassezia* cells is not mediated through a single pathway, as it has been shown that mast cell responses can be modulated by *Malassezia* through the canonical Toll-like receptor 2 (TLR2)/MyD88 pathway but also through a different, not-yet-determined one (282). Interestingly, the contact of *Malassezia* cells with serum and subsequent opsonization increased their ability to induce IL-8 expression in a macrophage cell line and a granulocytic cell line (304). The differential stimulation of cytokine, chemokine, and adhesion molecule expression in host effector cells (Table 9) would eventually lead to either up- or downregulation of skin inflammatory processes, probably depending on the modifying interactions of still poorly understood cofactors. The resulting deviations in the tissue milieu may be further reflected by the divergent pathophysiologic manifestations of *Malassezia*-associated skin conditions that span the whole spectrum between overt inflammatory responses (seborrheic dermatitis and atopic eczema) and a distinct absence of inflammation, as in pityriasis versicolor. It can be further speculated at this point that complex interactions between *Malassezia* yeasts and their commensal or pathogenic microbial bystanders on the skin surface may not only mutually affect the survival and virulence status of both but also serve as decisive modifying cofactors of the pathogenesis of all *Malassezia*-related skin diseases.

Conclusion

The interaction of *Malassezia* yeasts with the skin immune system is open to further research, and a prospective line of work would be analogous to that already under way for bacterial skin commensals. Species like *Staphylococcus epidermidis* have the ability to amplify the innate immune response through an increase in the constitutive expression of antimicrobial peptides, which are, however, active against the pathogenic species *Staphylococcus aureus* (328). A delineation of comparable interaction mechanisms would contribute to a better understanding of the significance of the reported differential colonization of lesional skin by distinctive, "pathogenic" *Malassezia* species subtypes compared to "nonvirulent" ones associated with healthy skin. Moreover, properly designed experiments could highlight the sequence of internal and external events in the skin microenvironment that mediates the development of *Malassezia*-associated diseases.

MALASSEZIA AND DISEASE

Pityriasis Versicolor

Pityriasis versicolor is the prototypical skin disease etiologically connected to *Malassezia* species. It is characterized by hypo- or hyperpigmented plaques that are covered by fine scales (*pityron*, Greek for scale), preferentially distributed in the so-called seborrheic areas of the skin surface, such as the back, chest, and neck (65) (Fig. 1). Vitiligo, pityriasis alba, and leprosy in corresponding areas of endemicity (211) are the main differential diagnoses of pityriasis versicolor. For the clinical differential diagnosis of this disease, Wood's light examination and the so-called "evoked-scale" sign (141, 284) have proven valuable. The latter sign consists of the provocation of visible scales by the stretching or scraping of a pityriasis versicolor lesion, by which the pathologically increased fragility of the lesional stratum corneum becomes evident. Although the exact structural alterations of the stratum cor-

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TABLE 6 Results from culture-based epidemiological studies of atopic eczema and psoriasis

Skin condition and reference	No. of patients/no. of positive cultures	% of cultures positive for:							Culture medium[a]	Location	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*			
Atopic eczema											
138	31/22	18	8	51	10	3	10		LNA	Canada	No. of CFU from cases of atopic eczema was significantly lower than that from healthy or pityriasis versicolor skin
344	60/31	16	22	32	21	3		6.5	LNA	South Korea	Trend in the severity of atopic eczema with *Malassezia* colonization was observed
277	124/69	28	3	46	4	7	30		LNA	Sweden	Mixed species were cultured in 11% of patients; healthy skin and seborrheic dermatitis skin were significantly more colonized than atopic eczema skin; *M. globosa* was significantly more common in atopic eczema skin
Psoriasis											
353	110/69	45	11	11	38				LNA	Iran	9% of patients had mixed cultures (>2 species); significant differences in isolation rates from psoriatic skin and healthy skin on the head
138	28/19	58		31		11.5			LNA	Canada	No. of CFU in psoriasis skin was significantly lower than those for other *Malassezia*-associated dermatoses; *Malassezia* grew more commonly on scalp and face than on arms and legs

[a] LNA, Leeming-Notman agar.

neum that lead to the increased fragility of the stratum corneum in pityriasis versicolor skin lesions are still unknown, it may be that the same aberrations could account for the partial disruption of epidermal barrier function and the increased transepidermal water loss observed for this disease (193). In the case of Wood lamp fluorescence, UV light is emitted at an approximately 365-nm wavelength, and the lesions of pityriasis versicolor will fluoresce reddish or yellowish green. Pityriasis versicolor does not permanently affect the structure of the lesional skin, although some cases that induced nonreversible skin atrophy have been reported (66, 269, 341). Histopathological examination of lesional skin biopsy specimens reveals a slight to moderate hyperkeratosis and, to a lesser degree, acanthosis. Depending on the extent of clinically manifested inflammation, the dermis contains a mild to almost absent superficial perivascular inflammatory cell infiltrate (Fig. 2) consisting mainly of lymphocytes, histiocytes, and, occasionally, plasma cells. Sometimes, mild melanin incontinence is observed. In the stratum corneum, there are numerous budding yeast cells and short hyphae (Fig. 2 and 3). Whether rare cases of pityriasis versicolor with interface dermatitis (Fig. 3) (302) are associated with the subsequent development of atrophying lesions is not known.

Pityriasis versicolor has been reported to appear in all age groups, ranging from infants 4 months old (84) to children (314), adults, and elderly individuals (85). However, the prevalence of this common skin disease is greater in the third and fourth decades of life, and its appearance is significantly affected by environmental factors such as temperature and humidity, patient immune status, and genetic predisposition. The annual incidence of pityriasis versicolor has been reported to range from 5.2% to 8.3% (93). Seasonal variations, although not consistent, are observed, with the highest incidence rates in September (314), spring and fall (55), or summer months (144). If not corrected for these variations, records on the prevalence of pityriasis versicolor in a population may be affected, but nevertheless, this disease is significantly more common in tropical and subtropical climates (93). The prevalence of the disease falls drastically in more temperate climates, as it was diagnosed in only 2.1% of young healthy males (mean age, 22 years) in Italy (156), with even lower rates in Sweden (0.5% of males and 0.3% of females) (147). The peak age-specific prevalence of pityriasis versicolor is among young adults 20 to 40 years old (189); however, in tropical/subtropical regions, such as India, the highest disease prevalence has been recorded for somewhat younger individuals, between 10 and 30 years old (89). Pityriasis versicolor is not an infectious disease, and hereditable factors decisively contribute to its appearance. A positive family history of pityriasis versicolor has been found for approximately 20% of patients (140, 144) in relevant studies without conjugal cases reported for married couples (144). Also, a polygenic additive-inheritance model of susceptibility to this disease was observed in one of these studies (144). The reported differences in the male-to-female ratio are suggestive of a sampling or reporting bias, as expected for a fluctuating disease without alerting symptoms. The burden of pityriasis versicolor might not be that evident in light-colored Caucasians but can represent social stigmatization when extensive depigmentation happens in colored skin.

Pityriasis versicolor and *Malassezia*. Besides the consistent description of yeasts from pityriasis versicolor lesions, there are two main facts that permit an etiologic association of *Malassezia* with this disease: (i) it is more likely that a positive culture will be

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TABLE 7 Epidemiological data for non-culture-based methods

Skin type and reference	No. of patients	% of cultures positive for:									Method(s) and target gene(s)[a]	Description
		M. globosa	*M. restricta*	*M. sympodialis*	*M. furfur*	*M. slooffiae*	*M. obtusa*	*M. dermatis*	*M. yamatoensis*	*M. japonica*		
Healthy												
308	20	100	92								Quantitative PCR targeting 26S rDNA and the ITS2 region	Healthy skin of psoriasis patients; only *M. globosa* and *M. restricta* were searched for
307	27	70	56	15		22		18.5	4	4	Nested PCR, real-time PCR targeting ITS1 and IGS1 regions	Healthy skin of seborrheic dermatitis patients
307	30	87	83	37	27	17	10	30	7	10	Nested PCR, real-time PCR targeting ITS1 and IGS1 regions	Healthy patients
295	18	44.5	61	50	11	7					Nested PCR targeting ITS1, ITS2, 5.5S rDNA	Healthy university students
Pityriasis versicolor												
224	49	94	94	35	10	8	4	24.5	4	6	Nested PCR, real-time PCR targeting ITS1 and IGS1 regions	Only *M. globosa* was detected in scales with hyphae by direct microscopy
Seborrheic dermatitis												
307	31	93.5	74	35.5	6.5	39	10	39	10	13	Nested PCR, real-time PCR targeting ITS1 and IGS1 regions	Lesional seborrheic dermatitis skin harbored 3 times more *Malassezia* populations than healthy skin
Atopic eczema												
344	60	16	22	32	21	3		6			PCR-restriction fragment length polymorphism, 26S rDNA	Mixed isolations were observed but not further analyzed; there was no significant difference between positive *Malassezia* cultures, isolated *Malassezia* species, and severity of atopic eczema
307	36	100	97	58	33	31	28	31	14	58	Nested PCR, real-time PCR targeting ITS1 and IGS1 regions	Atopic eczema skin was colonized more often than seborrheic dermatitis, pityriasis versicolor, or healthy skin
295	32	87.5	94	41	41						Nested PCR targeting ITS1, ITS2, 5.8S rDNA	*M. restricta*, *M. globosa*, and *M. furfur* DNAs were more commonly found in atopic eczema lesions than in controls; this was not found for *M. sympodialis*
298	34	30–35	45–51								qPCR targeting 26S rDNA and the ITS2 region	Only *M. globosa* and *M. restricta* were searched for; *Malassezia* colonized all atopic eczema patients, but the load on the head was 12.4 times higher than that on the trunk and 6.8 times higher than that on limbs
Psoriasis												
308	20	98	92									No correlation of psoriasis severity with *Malassezia* colonization; *Malassezia* load on the head was 10-40 times higher than that on the trunk; *M. restricta* was significantly more common than *M. globosa* in lesional skin of the head and limb; the other *Malassezia* species were not individually searched for
9	22	82	96	64	18	27	18	27	14	27	IGS, ITS	No difference in detection rate of *Malassezia* spp. between healthy and psoriasis skin and no associations with age, gender, site, severity, or treatment; psoriasis and atopic eczema skin presented higher levels of species variability

[a] ITS, internal transcribed spacer; IGS, intergenic spacer.

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TABLE 8 *Malassezia* species subtypes associated with skin diseases[a]

Malassezia sp. and reference	Method	Description
M. globosa		
112	PCR–single-strand conformational polymorphism of ITS1	*M. globosa* strains were distinguished into 5 subtypes; 1 was associated with extensive disease
307	IGS1 sequencing	8 groups were identified, 1 comprised of healthy strains, 5 comprised of seborrheic dermatitis and atopic eczema, and 2 comprised of healthy and seborrheic dermatitis strains
294	IGS1 sequencing	4 groups, 2 from atopic eczema, 1 healthy, and 1 healthy and atopic eczema mixed
M. restricta		
296	IGS1 sequencing	Strains from healthy individuals were distinguished from strains from atopic eczema patients and had fewer sequence repeats
307	IGS1 sequencing	A healthy skin group and a seborrheic dermatitis group were identified
247	Sequencing of 18S rDNA (partial), ITS1, 5.8S rDNA, ITS2, and 28S rDNA (partial)	Six sequence types were identified in building dust, and *Malassezia* yeasts were the most common isolates, especially in winter
M. sympodialis		
112	PCR–single-strand conformational polymorphism of ITS1	*M. sympodialis* displayed a uniform profile
109	PCR–single-strand conformational polymorphism of Mala s 1 sequences	*M. sympodialis* displayed a uniform profiles
38	Sequencing of D1 and D2 regions of 26S rDNA, ITS-5.8 rDNA	Isolates from different animals clustered within 4 groups, including *M dermatis* and *M. nana*
207	ITS1 sequencing	Subgroups in stock strains identified without clinical relevance
134	Amplified fragment length polymorphism	*M. sympodialis* displayed uniform profiles
M. furfur		
111	PCR-restriction fragment length polymorphism of ITS2	*M. furfur* strains of Greek origin presented an additional BanI restriction site compared to Bulgarian and CBS collection strains
125	26S D1/D2 sequencing, partial 5.8S and ITS2 region sequencing	Colombian *M. furfur* isolates with variable Tween assimilation profiles clustered into a distinct group
207	ITS1 sequencing	Subgroups in stock strains identified without clinical relevance
315	Amplified fragment length polymorphism	4 subgroups identified; 1 included systemic isolates from humans
117	PCR-random amplified polymorphic DNA	Pityriasis versicolor strains were differentiated from seborrheic dermatitis/seborrheic dermatitis-HIV strains
134	Amplified fragment length polymorphism	Strains from neonatal systemic infections and skin clustered into two distinct groups
350	PCR-fingerprinting (M13 primer)	*M. furfur* from Han and Tibetan volunteers clustered into different groups; also, skin disease associations were evident
88	PCR-random amplified polymorphic DNA (M13, OPA2, OPA4)	Only 5 strains of *M. furfur* were included, and some difference could be observed between human and cattle isolates
113	PCR-fingerprinting (M13 primer)	Greek, Bulgarian, and Scandinavian (permanent Greek residents) strains were categorized into distinct groups; within the Bulgarian cluster, seborrheic dermatitis strains were differentiated from pityriasis versicolor and dandruff strains
170	ITS1 sequencing	All isolates from blood culture bottles and catheter tips clustered into a single group
M. slooffiae		
88	PCR-random amplified polymorphic DNA (M13, OPA2, OPA4 primers)	OPA2 and OPA4 differentiated human from cattle isolates
M. pachydermatis		
207	ITS1 sequencing	Subgroups in stock strains identified without clinical relevance
3	*chs-2* sequencing, PCR-random amplified polymorphic DNA (FM1 primer)	Four subgroups were differentiated; good correlation between the 2 methods
46	LSU rDNA, ITS1, *chs-2* gene sequencing	3 major groups with lipid-dependent strains clustering in 2 of them, and non-lipid-dependent strains dispersed in all 3 groups; associations with origins of strains were highlighted

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TABLE 8 (Continued)

Malassezia sp. and reference	Method	Description
45	PCR–single-strand conformational polymorphism of the ITS1 region and *chs-2*	Typing was possible without any clinically relevant information retrieved
43	PCR–single-strand conformational polymorphism of the ITS1 region and *chs-2*	ITS1 region more variable than *chs-2* sequences; 3 major genotype groups distinguished, and 2 were associated with extensive disease and increased phospholipase activity, and 1 was associated with healthy skin and lower phospholipase activity
222	Multilocus enzyme electrophoresis	Considerable genetic variation corresponding to that revealed by partial LSU sequencing
4	PCR-random amplified polymorphic DNA (FM1 primer), *chs-2* sequencing	Low discriminatory potential due to the same origin of the strains (dog otitis)
49	PCR-random amplified polymorphic DNA (M13, OPT-20)	M13 primer did not differentiate groups; OPT-20 differentiated 4 groups, with 2 of them correlating with the external ear canal of dogs

[a] ITS, internal transcribed spacer; IGS, intergenic spacer; LSU, large subunit; *chs-2*, chitin synthase 2 gene.

obtained from specimens taken from lesional skin than from macroscopically unaffected skin areas of either the same individual (255) or matched healthy controls (275), and (ii) the hyphal state is connected to pityriasis versicolor lesions, independently of the *Malassezia* species isolated, and seems to play an important role in the pathogenesis of this disease (127). However, the expansion of hyphae in pityriasis versicolor patients is not confined to lesional skin. This points to a global propensity of the skin of these patients, at least at the time of overt disease, to support the hyphal growth of *Malassezia* species. Rates of isolation of hyphae from nonlesional trunk skin (42%) and the head (50%) of patients with pityriasis versicolor were lower than those reported for the lesions *per se* (100%) but were more than those reported for the skin of healthy individuals (6 to 7%) (217). As mentioned above, the *Malassezia* species initially associated with pityriasis versicolor was *M. globosa* (63), but current epidemiological data as well as the absence of distinct virulence factors confined to this species (151) do not permit a definite conclusion.

The involvement of *Malassezia* yeasts in the development of pityriasis versicolor illustrates the excellent adaptive mechanisms which this yeast possesses, with relevance to human skin physiology. In the two most common clinical forms of this disease, the hyperpigmented and hypopigmented forms, there is a significant fungal load on the skin but without any inflammatory alterations being observed. This has been partly attributed to the production of an array of indolic compounds produced by *Malassezia* species, in particular *M. furfur* (213), that have the ability to downregulate aspects of the inflammatory cascade (see below). Thus, indoles like pityriarubins impede the respiratory burst of human neutrophils (183), while indirubin and indolo[3,2-b]carbazole inhibit the phenotypic maturation of human dendritic cells (324). Additionally, malassezin was proposed to induce apoptosis in human melanocytes, and pityriacitrin was initially shown to have UV radiation-absorbing properties (206, 215). Due to its UV-absorbing capacity, it was proposed that it protects the underlying skin in the hypopigmented plaques of pityriasis versicolor (pityriasis versicolor alba) (190). However, this was not confirmed in subsequent *in vivo* and *in vitro* experiments (116), suggesting that additional substances may contribute to the clinically observed UV resistance of lesional skin. For the synthesis of these compounds, tryptophan aminotransferase, which converts L-tryptophan to indolepyruvate, has been inferred to be an important enzymatic step from data acquired from the phylogenetically close phytopathogenic yeast *Ustilago maydis* (355). The inhibition

of this enzyme by cycloserine led to the clinical reversal of hyperpigmented pityriasis versicolor lesions *in vivo* (214). The synthesis of these indoles is widely distributed among *Malassezia* species, and since this trait is also associated with the respective pathogenic potential of *M. furfur* (108) (P. Magiatis et al., unpublished data), the existence of additional biosynthetic pathways cannot be excluded.

Other metabolites that have been linked to the clinical presentation of pityriasis versicolor include melanin (107), azelaic acid (232), and other products of skin lipid peroxidation (80). The *in vitro* production of melanin by L-3,4-dihydroxyphenylalanine (L-DOPA) has been documented; however, the observation of melanized *Malassezia* cells *in vivo* in hyperpigmented lesions of pityriasis versicolor (107) still remains to be confirmed by relevant clinical studies. Finally, the proposed attribution of lesional skin hypopigmentation to the known competitive inhibition of tyrosinase activity by *Malassezia*-produced azelaic acid is most probably not relevant to the clinical setting, as this dicarboxylic acid cannot be synthesized in biologically significant quantities on diseased skin (196).

Treatment. As mentioned above in the introduction, treatment for pityriasis versicolor will be discussed only briefly, and readers are referred to a recent relevant meta-analysis for further details (153). The goal of both topical and systemic treatments of pityriasis versicolor is not to eradicate *Malassezia* from skin but to restore the yeast's population dynamics to the commensal status.

In general, longer treatment periods (up to 4 weeks) and higher concentrations of topical regimens or doses of systemic agents result in higher cure rates, without, however, avoiding the increased relapse rate (153). In the latter case, prophylactic treatment regimens have been suggested.

Topical treatments are generally well tolerated and highly effective compared to placebo. Among the topical regimens, shampoos containing fungicidal concentrations of antifungal imidazoles, applied once daily for up to 4 weeks, were found to be adequately effective for the treatment of pityriasis versicolor (83).

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TABLE 9 Effects of *Malassezia* interactions with cells[a]

Species	Reference	Growth medium	Ratio of no. of *Malassezia* cells/no. of cells	Substrate(s)	Growth factor(s) of innate immunity	Description
M. furfur	306	Dixon's agar	Live or heat-killed cells	Monocytic cell line (THP-1), granulocytic cell line (HL-60)	Up, IL-1α, IL-8; no change, IL-6, -8, and -12, TNF-α	ELISA and reverse transcription-PCR with visual comparison of the produced mRNA were employed, thus having restricted sensitivity; opsonized cells induced higher levels of IL-8 expression than did nonopsonized cells
M. furfur	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	No effect, IL-1β, IL-6, IL-8, TNF-α, MCP-1	No effect on expression of cytokines tested
M. furfur	28	SD + olive oil + Tween 80	30 to 1	HaCaT	Up, ICAM-1, IL-10, TGF-β1; down, IL-1α, TNF-α; no expression, IL-6	IL-6 was not expressed, and this was attributed to the downregulation of IL-1α and TNF-α
M. furfur	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	Up, IL-1β, IL-6, IL-8, TNF-α; no change, MCP-1	1-24 h of stimulation, efficient cytokine production when coincubation was done for >6 h; *M. furfur* and all culture supernatants had no effect on cytokine production
M. furfur	86	SD + olive oil + Tween 80	30 to 1	Normal human keratinocytes	Up, HBD-2, TGF-β1, IL-10	HBD-2 is protein kinase C dependent and has the ability to kill *M. furfur* cells at 50 μg/ml
M. furfur	27	SD + olive oil + Tween 80	30 to 1	Normal human keratinocytes	Up, TGF-β1, integrins (αv, β1, β3, β5), HSP70	Activating protein 1 was considered to mediate expression, as this effect was inhibited by curcumin
M. furfur	26	SD + olive oil + Tween 80	30 to 1	Normal human keratinocytes	Up, TLR2, MyD88, IL-8, HBD-2 and -3	TLR2-dependent increase in levels of HBD-2 and IL-8
M. furfur	161	LNA	20 to 1	PHK16-0b, normal human keratinocytes	No significant expression of cytokines by microarray analysis	Absence of a T-helper-2-polarizing response of keratinocytes was attributed to minor contribution of this species to atopic eczema
M. furfur	316	LN broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer; nonviable, stationary cells of *M. furfur* produced the highest increase in levels of IL-6
M. globosa	161	LNA	20 to 1	PHK16-0b, normal human epidermal keratinocytes	IL-3, IL-5, IL-6, IL-7, IL-10, IL-13, GM-CSF, IL-8, TIMP-1 and -2	Slightly lower expression levels of cytokines in human keratinocytes, with GM-CSF, IL-5, and IL-10 being the most significantly induced
M. globosa	316	LN broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer; viable, stationary cells produced the highest increase in levels of IL-8 after lipid capsule removal
M. globosa	160	LNA	20 to 1	Normal human keratinocytes	Thymic stromal lymphopoietin	Expression level of thymic stromal lymphopoietin was increased at higher calcium concentrations and was decreased when cells were treated with detergent
M. restricta	316	LN broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer; viable, stationary cells produced the second highest increase in IL-8 levels after lipid capsule removal
M. restricta	161	LNA	20 to 1	PHK16-0b, normal human epidermal keratinocytes	IL-4, monocyte inhibitory protein 3α, leptin, cutaneous-T-cell-attracting chemokine, placental growth factor	IL-4 was the only cytokine significantly expressed in normal human keratinocytes

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TABLE 9 (Continued)

Species	Reference	Growth medium	Ratio of no. of *Malassezia* cells/no. of cells	Substrate(s)	Growth factor(s) of innate immunity	Description
M. restricta	160	LNA	20 to 1	Normal human keratinocytes	Thymic stromal lymphopoietin	Expression level of thymic stromal lymphopoietin was increased at higher calcium concentrations and was decreased when cells were treated with detergent
M. slooffiae	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	Up, IL-1β, IL-6, IL-8, TNF-α; no change, MCP-1	Achieved lower levels expression of cytokines than *M. pachydermatis* and levels equivalent to those achieved by *M. sympodialis*; culture supernatants had no effect
M. slooffiae	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	Up, IL-1β, IL-6, IL-8, TNF-α; no change, MCP-1	1-24 h of stimulation, efficient cytokine production at >6 h of coincubation; culture supernatants had no effect on cytokine production
M. slooffiae	316	LN broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer
M. sympodialis	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	Up, IL-1β, IL-6, IL-8, TNF-α; no change, MCP-1	Achieved lower levels of expression of cytokines than *M. pachydermatis* and levels comparable to those of *M. sympodialis*; culture supernatants had no effect
M. sympodialis	161	LNA	20 to 1	PHK16-0b, NHEK	IL-6, bone morphogenetic protein 6	Absence of a T- helper-2-polarizing response of keratinocytes was attributed to the minor contribution of this species to atopic eczema
M. sympodialis	316	LN Broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer
M. sympodialis	282		Whole extract	Bone marrow-derived mouse mast cells	Up, cysteinyl leukotrienes, IL-6, MCP-1	The extract increased the level of production of cysteinyl leukotrienes in non-IgE-sensitized cells and IgE-mediated degranulation, IL-6, and ERK phosphorylation in IgE receptor-cross-linked cells; this activation was TLR2/MyD88 dependent and independent
M. sympodialis	264		*M. sympodialis* extract	Bone marrow-derived mouse mast cells	Up, IL-6, IL-8, TLR-2, dectin-1	Mast cells from atopic dermatitis patients demonstrated a defective expression of dectin-1 and an enhanced response to *M. sympodialis*
M. obtusa	316	LN broth	27 to 1	Normal human keratinocytes	Up, IL-1α, IL-6, IL-8, IL-10; no change, TNF-α	Stimulation of cytokine production depended on species, growth phase (exponential vs stationary), and removal of the lipid layer; *M. obtusa* caused the second highest level of IL-6 production with nonviable, stationary cells after removal of the lipid layer
M. pachydermatis	329	SD liquid + Tween 40	1 to 1	Normal human keratinocytes	Up, IL-1β, IL-6, IL-8, TNF-α; no change, MCP-1	Achieved the highest levels of expression of cytokines compared to those of *M. sympodialis* and *M. slooffiae*; culture supernatants had no effect
M. pachydermatis	340	Potato dextrose agar with olive oil	Increasing concentrations	Bone marrow-derived macrophages	Up, TNF-α, MIP-2, KC, IL-10	Part of the induction of these cytokines was through the activation of Mincle

[a] SD, Sabouraud dextrose agar; IL, interleukin; TNF-α, tumor necrosis factor alpha; ICAM-1: intercellular adhesion molecule 1; TGF, transforming growth factor; MCP-1, monocyte chemotactic protein 1; HBD, human beta defensin; HSP70, heat shock protein 70; TLR2, Toll-like receptor 2; LNA, Leeming-Notman agar; LN, Leeming-Notman; GM-CSF, granulocyte-monocyte colony-stimulating factor; TIMP-1, tissue inhibitor of metalloproteinase 1; ELISA, enzyme-linked immunosorbent assay.

However, older studies also documented that nonimidazole topical agent formulations (zinc pyrithione shampoo, sulfur-salicylic acid shampoo, and selenium sulfide lotion) are sufficiently effective treatment options compared to placebo (21, 104, 276). More recently, pathophysiologically designed topical therapeutic approaches that target certain aspects of pityriasis versicolor pathogenesis are under clinical evaluation. Among them, quite promising approaches seem to be a 10-day application of a nitric oxide-liberating cream (168); the application twice daily of a 0.2 mol liter^{-1} aqueous cycloserine solution for 5 days, which resulted in the complete healing of hyperpigmented pityriasis versicolor with a rapid correction of the pigment deviation (214); and

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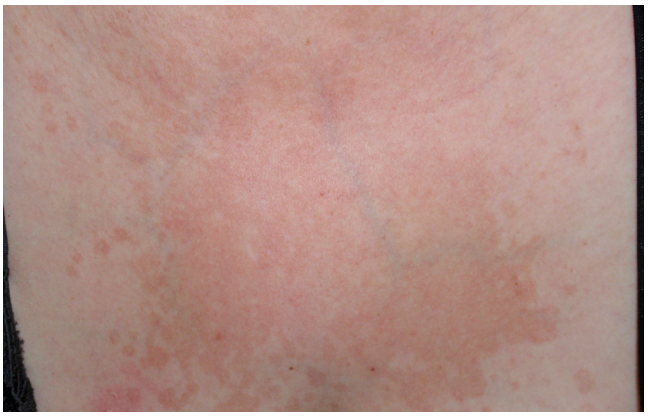

FIG 1 Pityriasis versicolor in a 42-year-old female patient. The patient had relapsing disease for the past 6 years.

5-aminolevulinic acid photodynamic therapy for regionally confined lesions (179).

Extensive pityriasis versicolor can be treated successfully and safely with different oral antifungals (ketoconazole, itraconazole, and fluconazole) applied at a rather wide range of doses (range of up to 4×) and for treatment periods of 7 to 28 days (153). This is also the case with the use of newer imidazoles, like pramiconazole (100). Currently, the efficacy of single-dose regimens with different oral imidazoles to improve compliance is under clinical evaluation (78, 326).

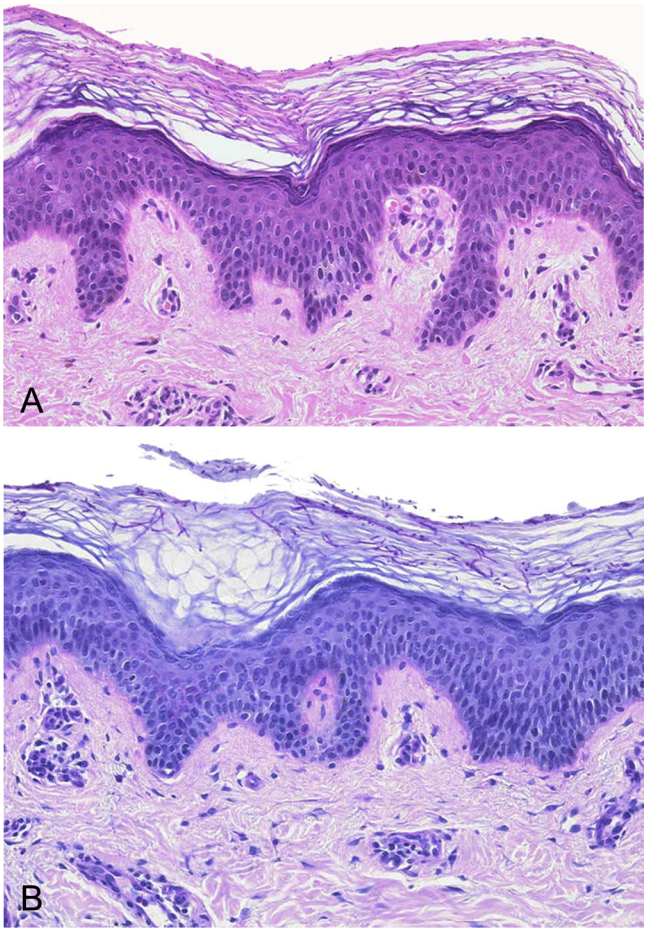

FIG 2 Histopathology of noninflammatory pityriasis versicolor. Shown is the infiltration of the hyperkeratotic stratum corneum by *Malassezia* cells and hyphae; there is a distinct absence of an inflammatory cell infiltrate. (A) Hematoxylin-eosin stain; (B) PAS stain. Original magnification, ×200.

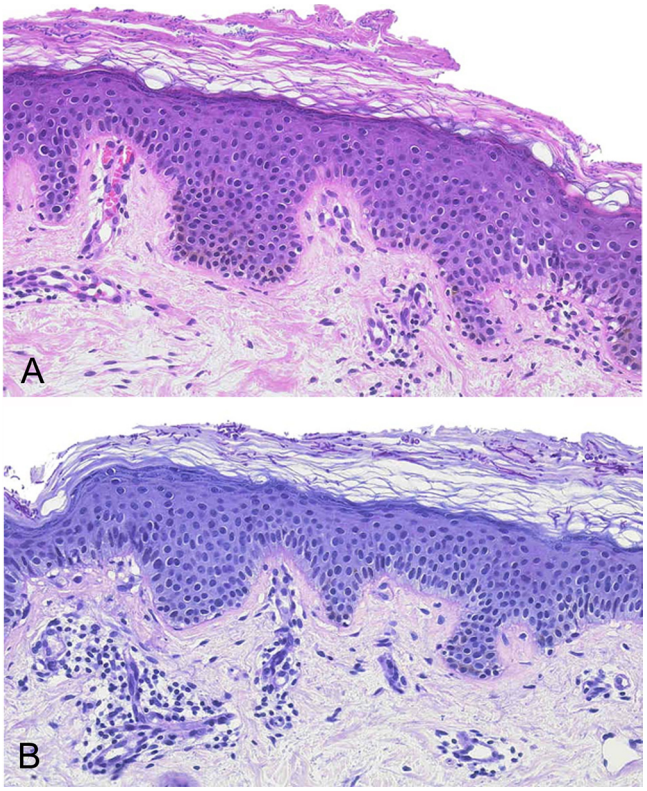

FIG 3 Histopathology of inflammatory pityriasis versicolor. Shown is the infiltration of the hyperkeratotic stratum corneum by *Malassezia* cells and hyphae; there is a moderately dense perivascular inflammatory cell infiltrate in the upper dermis. (A) Hematoxylin-eosin stain; (B) PAS stain. Original magnification, ×200.

Pityriasis versicolor prophylaxis approaches are not well documented. Two older trials reported that itraconazole at 200 mg twice daily, once per month, sufficiently reduced the rate of disease relapses compared to placebo (see reference 153). Optimal preventive regimens employing other oral antifungals or topical formulations have not been adequately evaluated to date.

Conclusion. The relationship between pityriasis versicolor and *Malassezia* still remains an obscure one despite the frequency of this skin disease and the confirmed association with *Malassezia*. However, dissecting the mechanisms that trigger this skin disease would expand our knowledge on *Malassezia* and skin adaptive homeostatic mechanisms.

Seborrheic Dermatitis

Seborrheic dermatitis (synonym, seborrheic eczema) is a relapsing skin disease that shows a predilection for the so-called seborrheic areas of the skin, such as the scalp, eyebrows, paranasal folds (Fig. 4), chest, back, axillae, and genitals, and is characterized by recurrent erythema and scaling. However, it should also be stressed that despite its designation, seborrhea is not present in seborrheic der-

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FIG 4 Seborrheic dermatitis in the nasolabial folds. The distribution of the lesions is typical; however, the seborrheic dermatitis can be characterized as severe, as the disease is extended into the parietal region and is associated with intense erythema and scaling.

matitis (37). No widely accepted criteria regarding the diagnosis and grading of seborrheic dermatitis exist, and identification can constitute a clinical problem for psoriasis patients with facial involvement, a condition termed sebopsoriasis. Seborrheic dermatitis was initially described by Unna (318), and the association with *Malassezia* yeasts was accepted up to the middle of the 20th century, when the observed increased epidermal cell turnover gradually prompted researchers to characterize this condition as being intrinsic to the skin, analogous to psoriasis. The recognition of the role of *Malassezia* yeasts in seborrheic dermatitis pathogenesis was reappraised in the 1980s, when it was shown that the common denominator of the multiple treatment regimens used for seborrheic dermatitis was their antifungal activity (288).

The prevalence of seborrheic dermatitis is high, reaching 11.6% in a study from the United States, while dermatologists had diagnosed this condition in 2.6% of men and 3.0% of women in a relevant study (229). The disease is more common in certain populations, such as the elderly (181), and can be severe and therapy resistant in neuroleptic-induced Parkinsonism (31) and HIV patients (227). The occasionally observed clinical resistance to azole drugs in some cases of seborrheic dermatitis could be attributed to variable genotypes of the recently described *M. globosa* azole-metabolizing CYP51 enzyme (177).

The prevalence of seborrheic dermatitis peaks when sebaceous gland activity is high (15), during the first 3 months of life (infantile seborrheic dermatitis) and during puberty, but also when sebum excretion is reduced after the age of 50 years (61). Seborrheic dermatitis flares are also observed in the fall, when the level of sebum production is decreased compared to that in summer (345). The flare of disease could be associated with altered population dynamics, which would be affected not only by variations in sebaceous gland activity but also by modifications in other nutrients supplied by sweat, such as essential amino acids like glycine and tryptophan (148). It has been shown *in vitro* that glycine stimulates the fast growth of *M. furfur*, and when this amino acid is exhausted, yeast cells employ tryptophan as a nitrogen source, increasing the production of indolic metabolites (24). Such cycles of population growth, bioactive indole production, and subsequent deprivation of nutrients could result in insufficiently masked antigens and ligands on the surface of the yeast cells, which would result in the activation of the immune system. One study showed that increased numbers of metabolically active cells during summer resulted in higher rates of isolation in culture medium than in fall, although the actual DNA loads were equal in both seasons (6). The difference in the rates of active versus stationary/dead yeasts cells would result in the differential regulation of the skin immune response (316).

Seborrheic dermatitis and *Malassezia*. Currently available data are not sufficient to define *Malassezia* virulence factors that lead to the appearance or exacerbation of seborrheic dermatitis. It should be noted that skin is the niche of *Malassezia*, and the interplay of the yeast with keratinocytes and immune cells determines the transformation of this commensal to a pathogen.

Environmental factors, such as UV radiation and antagonistic microorganisms, may constitute stress factors similarly for *Malassezia* yeasts and the skin. Thus, the ability of *Malassezia* to locally modify the immune response, in addition to host susceptibility and the production of secondary metabolites by the yeast, probably participates in eliciting and maintaining seborrheic dermatitis. Higher production rates of aryl hydrocarbon receptor (AhR) ligands *in vitro* by *M. furfur* have been associated with seborrheic dermatitis isolates (108). AhR is found in sebocytes (169), and its function is modified by epidermal growth factor receptor (EGFR) (268, 301). The latter probably has a seborrheic distribution, as antibodies or small molecules that block its function cause a folliculocentric eruption with a seborrheic distribution (36), and the interplay of these two receptors was proposed previously (105). Thus, an initial approach to understanding the participation of aryl hydrocarbon receptor in seborrheic dermatitis would be to study polymorphisms of the implicated downstream proteins (218) in patients and healthy controls and associate them with the indole-producing capacity of *Malassezia* strains that are isolated from their skin.

Current evidence demonstrates that seborrheic dermatitis results from a nonspecific immune response to *Malassezia* yeasts. Unfortunately, very few experiments were performed after the identification of new *Malassezia* species, and this is reflected in the available data (Table 9). Inflammatory markers recorded by immunocytochemistry of skin biopsy specimens from seborrheic dermatitis lesions show an increase in levels of inflammatory mediators (interleukin-1α [IL-1α], IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, gamma interferon [IFN-γ], and tumor necrosis factor alpha [TNF-α]) in the epidermis and around the follicles of diseased skin (98). These inflammatory markers are equivalent to those produced by *Malassezia* yeasts in experimental models (Table 9). However, this increase did not differ statistically from levels in adjacent, healthy-looking skin and varied only from levels on the skin of healthy volunteers (98), suggesting an individual susceptibility to the development of seborrheic dermatitis. Furthermore, *Malassezia* yeasts demonstrated an ability to induce immune reactions, depending on the species, the culture growth phase, yeast cell viability, and the integrity of *Malassezia* cells (316) (Table 9). The 2 species that are commonly isolated from human skin (*M. globosa* and *M. restricta*) demonstrate distinct profiles of proinflammatory cytokine production from epidermal cells, with *M. globosa* stimulating the production of significantly more cytokines than *M. restricta*. However, the net effect of this cytokine synthesis, i.e., immune stimulation or tolerance, cannot be extracted from published data, as experimental conditions are not comparable (Table 9). For example, even the use of different culture media could result in different compositions of the lipid layer that covers the cell wall of *Malassezia*, resulting in a variable modulation of the immune system (316). In a recent study, the levels of binding and activation of the C-type lectin Mincle caused by *Malassezia* yeasts

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were higher than those of other fungi (340). However, the growth of *Malassezia* yeasts in a medium with only olive oil as a lipid source would have resulted in an insufficient masking of mannose residues that could subsequently be recognized by Mincle (340).

Another virulence factor intrinsic to *Malassezia* yeasts that has been discussed in association with the pathogenesis of seborrheic dermatitis is the production of phospholipases and the response to β-endorphin. The increased level of production of phospholipase after β-endorphin stimulation has been shown only for pathogenic *M. pachydermatis* strains; however, there is evidence that this also applies to lipophilic *Malassezia* species, although to date, this has been reproducible *in vitro* only for *M. furfur* (323). However, sebum production is increased by β-endorphin (354), and the demonstration of a functional μ-opioid receptor in pathogenic and nonpathogenic *M. pachydermatis* strains (41, 42, 44) has been shown. This points toward the existence of an equivalent sensory pathway in the lipophilic *Malassezia* species that could assist in the preparation of the yeast for a better utilization of sebaceous lipids. The aberrant production of *Malassezia* phospholipases on the skin could result in the removal of epidermal lipids, disruption of the epidermal barrier function, and the development of seborrheic dermatitis when sebum production is constitutionally decreased. Phospholipase production is a well-established virulence factor in *Candida albicans* (187), and the existence of environmental sensory G-protein-coupled receptors in fungi has been shown (339). Mining of the sequenced genome of *M. globosa* would lead to the recognition and detection of relevant genes in *Malassezia* and their association with the pathogenetic potential of the respective strains.

***Malassezia*, seborrheic dermatitis, and HIV/AIDS.** Seborrheic dermatitis in HIV/AIDS patients is more severe and more recalcitrant to treatment and advances with the stage of the disease (227). HIV/AIDS is associated with the development of multiple skin diseases; however, seborrheic dermatitis is the most common, with its reported prevalence ranging between 20 and 40% in HIV-1-seropositive patients and between 40 and 80% in those with AIDS (317). The keratinocyte response to stress signals (258) as well as the cross talk of Langerhans cells with CD-4 memory lymphocytes are modified in HIV/AIDS patients, and the skin immune system is disorganized by the destruction of both subsets of immune cells (249). Data from *Malassezia* population studies of HIV/AIDS-associated seborrheic dermatitis are inconclusive, as increased numbers of *Malassezia* yeasts have been found on the skin of HIV/AIDS-positive volunteers without seborrheic dermatitis (245) and on the healthy skin of HIV-positive seborrheic dermatitis patients (245) compared to controls. However, decreased *Malassezia* numbers in HIV patients with seborrheic dermatitis (227, 335) have also been reported, calling into question the implication of *Malassezia* yeasts (335). It is conceivable that as HIV/AIDS advances, the skin immune system disintegrates and, therefore, multiple treatment-resistant viral, bacterial, and fungal dermatoses develop (165), challenging the survival of commensal *Malassezia* yeasts and prompting them to express virulence factors.

***Malassezia* and infantile seborrheic dermatitis.** Infantile seborrheic dermatitis describes a characteristic, usually nonpruritic, eczematous or psoriasiform eruption that usually appears between the second week and the sixth month of life and can involve the face, scalp, trunk, and sternum area, individually or in any combination (15, 343). The lesions might coalesce, especially on the face and flexures, but when on the trunk, they are more distinct. The microbial flora of the mothers seems to pass to the lactating infant during breastfeeding and readily colonizes the skin within the first 24 h of life (G. Stamatas, unpublished data). During rapid expansion in order to cover the infant skin biocene (i.e., the absence of living microorganisms), the interaction with the still immature neonatal immune system and the epidermis, itself adapting to its new environment, could cause seborrheic dermatitis.

***Malassezia* and dandruff.** Dandruff is a poorly defined, frequent, pathological skin condition confined to the scalp and is characterized by flaking with minimal to absent inflammation. Dandruff improves after reducing the population of *Malassezia* yeasts on the scalp with proper treatment (133). However, the experimental application of oleic acid has resulted in the production of dandruff lesions only in dandruff-prone individuals (75). Oleic acid in the scalp is produced from the hydrolysis of triglycerides by *Malassezia* lipases (74). A variety of lipases has been shown to be encoded by *M. furfur* (35), *M. pachydermatis* (285), and *M. globosa* (76). The expression of *M. globosa* lipases on the scalp of humans has been shown (76), increasing the significance of this observation and supporting a link between clinical observations (75) and experimental data (35, 76, 285).

Conclusion. Current data highly implicate *Malassezia* yeasts in the pathogenesis of both seborrheic dermatitis and dandruff. However, despite the global distribution and significant economic burden that these skin conditions inflict, amazingly, limited research has been conducted to date to improve our knowledge concerning the exact role of *Malassezia* in their pathogenesis. Nevertheless, both seborrheic dermatitis and dandruff represent excellent models for understanding the species- and strain-specific metabolic and immunogenic potential of *Malassezia* yeasts as well as host susceptibility.

Atopic Eczema

Atopic eczema (166) is a multifactorial skin disease with a diverse genetic background, and it is characterized by a distinct constellation of clinical symptoms and signs. Currently, the interplay between an inherently defective skin barrier (60) and an aberrant skin immune response (77) constitutes the most widely accepted pathophysiological concept for the understanding of the pathogenesis of this skin disease. *Malassezia* yeasts have species- and strain-specific properties that support a distinctive, probably more than simply modifying, role in the pathogenesis and maintenance of atopic eczema. Despite the fact that there is no definite conclusion regarding the timing of events that result in the development of atopic eczema (a barrier defect predisposes one to immune stimulation, or an immune defect causes barrier damage) (30), resident *Malassezia* yeasts could actively participate in the deregulation of the skin homeostatic mechanisms.

***Malassezia* and atopic eczema.** The anatomical substrate of the epidermal barrier function, which is defective in atopic eczema (60), is the stratum corneum of the epidermis, a thin biological membrane that covers the whole body surface. It is made up of the keratinized, terminally differentiated epidermal keratinocytes of the interfollicular epidermis bound together by corneodesmosomes, filled with natural moisturizing factor and embedded in a lipidic matrix that is composed mainly of ceramides, cholesterol, fatty acids, and cholesterol esters (60). The natural moisturizing factor is formed by the degradation of fillagrin, comprising sub-

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TABLE 10 *Malassezia* allergens

Allergen	Probable function[a]	Molecular mass (kDa)	Description	Reference(s)
Mala f 2	Peroxisomal membrane protein	21	Identified in 71.9% of atopic eczema patients sensitized to *M. furfur*	325
Mala f 3	Peroxisomal membrane protein	20	Identified in 70.3% of atopic eczema patients sensitized to *M. furfur*	325
Mala f 4	Mitochondrial malate dehydrogenase	35	Identified in 83.3% of atopic eczema patients; in this cohort of patients, the corresponding rate of sensitization for Mala f 2 was 88.8%	239
Mala s 1	Unknown	36		267
Mala s 5	Peroxisomal membrane protein	18		123
Mala s 6	Cyclophilin	60	30% of patients with atopic eczema or allergic bronchopulmonary aspergillosis have cross-reactive IgE against the recombinant protein	123
Mala s 7	Unknown	16		331
Mala s 8	Unknown	18		331
Mala s 9	Unknown	14		331
Mala s 10	Heat shock protein 70	86	69% IgE binding in serum of atopic eczema patients	10
Mala s 11	MnSOD	23	36% of atopic eczema patients were sensitized to recombinant Mala s 11 and presented cross-reactivity to human MnSOD; 75% IgE binding in serum of atopic eczema patients; demonstration of IgE binding residues in mutated Mala s 11; human MnSOD may have additional IgE binding epitopes not present in Mala s 11	10, 279, 321
Mala s 12	GMC oxidoreductase	67	Cell surface antigen; it is a major antigen, and 62% of atopic eczema patients have binding IgE antibodies; no alcohol substrate could be identified; it is expressed and released in culture medium in higher quantities at pH 6.1	348
Mala s 13	Thioredoxin	13	45% sequence identity with human thioredoxin; release of immediate-type allergic skin reactions in sensitized individuals; specific T lymphocytes for Mala s 13 were generated from patients with atopic eczema and not controls and cross-reacted with human thioredoxin	20, 199
MGp42	Heat shock protein 70	42	No cross-reactivity with human HSP70 despite high level of sequence homology (65%); low level of sequence homology with Mala s 10 (22%)	159

[a] MnSOD, manganese superoxide dismutase; GMC, glucose-methanol-choline.

stances such as lactic acid, sodium pyrrolidone, carboxylic acid, urocanic acid, and urea (60). Decisive for the proper function of the stratum corneum is the maintenance of a pH gradient between its acidic outer and basic inner surfaces that motors many vital functions of this life-imperative biological membrane. Constitutional genetic defects in the formation of this barrier can be aggravated by the action of commensal organisms like *Malassezia* yeasts. The production of proteinase and phospholipase has been shown for the mainly animal *M. pachydermatis* isolates (62) and has been correlated with disease severity in dogs (205). Furthermore, phospholipase production as a response to β-endorphin stimulation, possibly through the expression of β-opioid-sensing receptors, has also been shown for *M. pachydermatis* (42) but has not been confirmed for human lipophilic isolates (323). However, the production of multiple secreted lipases by *M. globosa*, as predicted by recent sequencing results (338), suggests the presence of an enzymatic mechanism that, in addition to utilizing the secreted sebum lipids, could further downgrade (74) the already compromised lipidic constituents of the atopic epidermal barrier.

The damaged epidermal barrier function coupled with the vicious itching-and-scratching cycle in atopic eczema would allow the penetration of whole and fragmented cells that could activate innate immunity and sensitize adaptive immunity in these patients (77, 334). As mentioned above, *Malassezia* yeasts stimulate keratinocytes to produce a variety of cytokines in a species-dependent manner (Table 9). When healthy-looking atopic skin was patch tested with *M. sympodialis* ATCC 42132 extract, it demonstrated a gene expression profile similar to that of diseased skin (273). This profile showed increased levels of expression of inflammation- and immune function-associated genes and the downregulation of genes associated with skin lipid production in samples taken from both sites. Overall, these data show that at least *M. sympodialis* has the ability to induce an atopic eczema profile *in vivo* in susceptible individuals.

At some point in the evolution of disease in an individual with atopic eczema, sensitization to *Malassezia* allergens can occur with the production of *Malassezia*-specific IgE (Table 10). The level of total IgE in the serum of subjects with atopic eczema correlates with disease severity and currently permits the discrimination of 2 clinical types of atopic eczema according to IgE levels, "extrinsic" and "intrinsic" atopic eczema (30), with high and low levels of IgE antibodies, respectively. The progression of the latter form to the former is considered possible during the course of the disease. Notably, sensitization to *M. sympodialis* may happen in atopic eczema patients with both forms of the disease. Furthermore, sensitization to *Malassezia* yeasts is specific for the skin manifestations of this disease and does not happen in atopic patients with mostly respiratory symptoms like rhinoconjuctivitis and/or asthma or in patients with other hypersensitivity skin syndromes, like urticaria (48). The extent of this sensitization varies according

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to the recombinant allergen used for testing and is greater for antigens that could present higher degrees of cross-reactivity with human proteins, such as Mala s 6, which demonstrates structural similarity with cyclophilin (Table 10). It was recently shown that the *M. sympodialis* allergen Mala s 13 (thioredoxin) can cross-react with human recombinant thioredoxin, stimulating skin and peripheral blood lymphocytes toward a Th1, Th2, and Th17 inflammatory phenotype. In *M. sympodialis*-sensitized atopic eczema patients (20), these cells not only cross-react with human thioredoxin but also express skin homing markers. Furthermore, when human skin keratinocytes were exposed to a variety of cytokines (gamma interferon, tumor necrosis factor alpha, and interleukin-4), they released significant quantities of thioredoxin into the medium, pointing toward an additional triggering pathway of atopic eczema in this group of patients (20).

***Malassezia* allergens.** IgE binding allergens have been identified in *M. sympodialis*, *M. furfur*, and, lately, *M. globosa* (Table 10). Although *M. globosa* is the most common species on human skin, and most atopic eczema patients present IgE reactivity to *M. globosa* antigens (347), only recently has research work focused on the identification and isolation of relevant allergens (159). The identified allergen, provisionally termed MGp42, has a molecular mass of 42 kDa and reacted with the sera of all atopic patients included in that study. This allergen corresponds to heat shock protein 70 (HSP70) of yeast, and interestingly, it demonstrates a higher level of sequence identity to the human (65%) or *Penicillium citrinum* (75%) protein than to the analogous *M. sympodialis* Mala s 10 allergen (22% sequence identity). However, despite the significant structural homology, further testing of MGp42 could not demonstrate noteworthy cross-reactivity with human HSP70, which was attributed to alterations in binding epitopes due to steric hindrance (159).

The best-studied *Malassezia* allergens are those identified for *M. sympodialis* (Table 10), and two types of these can be distinguished. The first type demonstrates sequence similarity to human proteins (Mala s 5, 6, and 10 to 13 and Mala f 2, 3, and 4) and cross-reactivity with relevant human proteins, and the second type (Mala s 1 and 7 to 9) demonstrates no similarity with any known protein, and thus, their function cannot be determined (110). Among the described *M. sympodialis* allergens, Mala s 11 possesses a high degree of sequence identity to the human mitochondrial enzyme manganese superoxide dismutase as well as to the homologous *Aspergillus fumigatus* enzyme (321). The residues that are responsible for IgE binding have been shown to partly correlate with those of the human enzyme (321). The complexity of the genus *Malassezia* is further highlighted by the structure of the major allergen of *M. sympodialis*, termed Mala s 1. This allergen has sequences that are found only in this particular species (109) and also demonstrates a crystallized 6-fold-β-propeller structure, a novel fold among allergens (322).

Conclusion. The implication of *Malassezia* yeasts in atopic eczema is currently under intense investigation, and more studies are needed in order to understand the exact role of these organisms in disease courses and exacerbations. However, the recognition of IgE binding allergens produced by *Malassezia* yeasts and the observed selectivity of the response of immune cells to *Malassezia* point toward a close association between the skin and its predominant eukaryotic symbiont.

Psoriasis

The association of *Malassezia* yeasts with psoriasis was first proposed by Rivolta (266), with a description of *Cryptococcus psoriasis* isolated from the epidermis of psoriasis patients. The yeast was described as double-contoured budding cells, later considered to correspond to *Malassezia* yeasts. However, the complexity of psoriasis pathogenesis and the ambiguous therapeutic potential of antimycotic drugs support only a secondary role, possibly that of an exacerbating factor, for *Malassezia* yeasts in psoriasis. Patch testing with sonication-killed *M. furfur* cells in psoriatic patients and controls succeeded in activating the disease in 10/10 patients, in comparison to 2/10 controls (202). In a psoriatic patient, guttate psoriatic lesions with compatible histology appeared in pityriasis versicolor lesions and subsided after fluconazole treatment (230). In another case report, guttate lesions of psoriasis developed in areas of *Malassezia* folliculitis (92). Also, the reverse has been observed, with recurrence of pityriasis versicolor after the healing of psoriasis following treatment with etanercept (198). However, the initial encouraging results for the treatment of scalp psoriasis with antifungal drugs (101, 271) have not been established in subsequent studies.

As mentioned above, epidemiological data on the distribution of *Malassezia* species in psoriasis lesional skin are contradictory (Tables 6 and 7), and diminished *Malassezia* numbers have been reported for healthy-looking and lesional skin of psoriasis patients (243, 244, 353). Also, pathogenic strains, like those established for pityriasis versicolor, atopic eczema, and seborrheic dermatitis, have not been found in cases of psoriasis (244). A possible explanation for this could be the relative scarcity of studies compared to the number of studies on other *Malassezia*-associated skin diseases. However, the recent pathogenesis model of psoriasis in genetically susceptible individuals includes the triggering of lesions by complexes formed from self-DNA released by stressed keratinocytes and the cathelicidin antimicrobial peptide LL-37, which subsequently stimulates plasmacytoid dendritic cells to secrete IFN-α, thus initiating and sustaining psoriasis lesions (234). A constitutionally excess production of antimicrobial peptides by psoriatic keratinocytes could be responsible for the diminished *Malassezia* population on psoriatic skin, but on the other hand, their production could also be secondarily exaggerated by *Malassezia* yeasts invading the skin and stressing predisposed keratinocytes (28). Thus, the resulting increase in the level of production of LL-37 (2) might contribute to the triggering of psoriasis lesions. Furthermore, the activation of TLR2 in keratinocytes seems to participate in the pathogenesis of psoriasis, most probably through the above-mentioned cathelicidin pathway. *Malassezia* yeasts have been shown to induce the TLR2 pathway (26). However, only to demonstrate the complexity of the participation of *Malassezia* yeasts in psoriasis pathogenesis, indirubin, a *Malassezia*-synthesized indole, was successfully employed for the treatment of this disease (200).

In conclusion, the role of *Malassezia* yeasts in exacerbations of psoriasis, especially on the scalp, will move in parallel with the eventual unraveling of the cause of psoriasis pathogenesis and the virulence characteristics of this yeast.

Malassezia Folliculitis

Malassezia folliculitis appears in the upper trunk, i.e., shoulders, back, and chest, and pruritus is a frequent symptom (Fig. 5). Oc-

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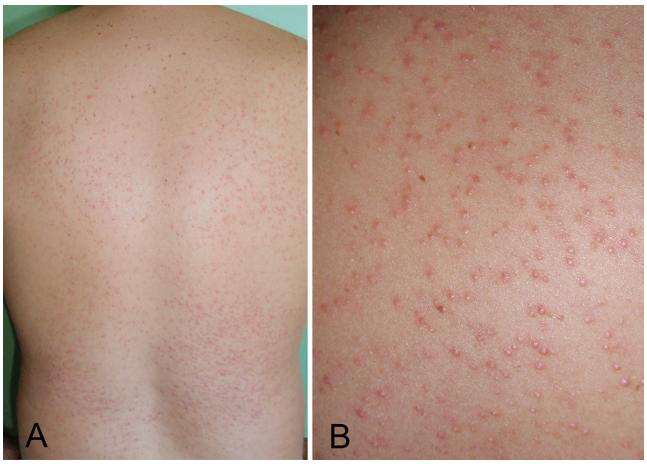

FIG 5 *Malassezia* folliculitis in a 34-year-old construction worker. The condition developed after working in a hot, humid environment for a few days. (A) Back of the patient. (B) Close-up view of the lesions.

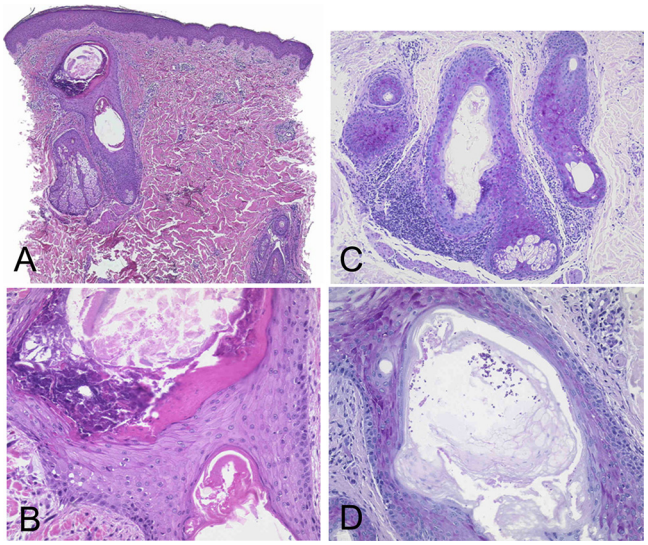

FIG 6 Histopathology of *Malassezia* folliculitis. (A) Dilated hair follicle filled with keratinous material and basophilic debris. Shown is a perifollicular inflammatory cell infiltrate with hematoxylin-eosin staining. Original magnification, ×40. (B) Detail of panel A showing hardly recognizable yeast cells in this section in keratinous masses within the infundibular lumen adjacent to the site of wall destruction. Hematoxylin-eosin staining is shown. Original magnification, ×200. (C) Dense perifollicular chronic inflammatory cell infiltrate with amorphous mucinous material in the dilated follicle lumen and PAS stain-positive tiny budding yeasts. PAS staining was used. Original magnification, ×100. (D) Detail of a serial section of the same follicle demonstrating numerous yeast spores within the dilated follicle lumen. PAS staining was used. Original magnification, ×200.

clusion is a common predisposing factor (18), especially for susceptible individuals (126), and the condition is also associated with immunosuppression (8, 226, 263); however, in these patients, it may appear with less distinct pruritus (65). Histopathological sections reveal dilated, partly destructed hair follicles, which contain keratinous material, debris, and, sometimes, mucin. Usually, a mild to moderate chronic inflammatory cell infiltrate encapsulates the infundibular portion of the affected follicle (Fig. 6). On periodic acid-Schiff (PAS)-stained sections, the presence of *Malassezia* yeasts becomes evident in the form of small spherical-to-oval yeast organisms without the regular observation of hyphae (250). There seems to be some predisposition to the development of *Malassezia* folliculitis along with other *Malassezia*-associated diseases like pityriasis versicolor and seborrheic dermatitis (99). It is more common in hot and humid environments and has been reported to coexist in 56% of acne patients in the Philippines (163) and to be present in 1 to 1.5% of dermatology outpatients in China (36). Thus, because of clinical similarities, this condition might be underdiagnosed in patients with acne (16). Also, *Malassezia* folliculitis in the form of an epidemic in an intensive care setting (12) and in heart transplant recipients (263) has been reported. However, it is rather rare in pregnancy (186), despite the corresponding relative immunosuppression.

The pathogenesis of *Malassezia* folliculitis is incompletely understood, but recent evidence shows that it is the normal cutaneous flora that infects the hair follicle and leads to the development of folliculitis (5). Thus, the most common species identified are *M. restricta*, *M. globosa*, and *M. sympodialis*, either alone or in association with each other (5). An older report assessing the use of ketoconazole for *Malassezia* folliculitis attributed the observed therapeutic effectiveness to the reversal of the follicular occlusion from the drug and not to its antifungal effects (149). In the future, studying the population of patients who develop *Malassezia* folliculitis under modern biologic therapies, pharmaceutical agents that also intervene with complex cellular signals, might prove more effective for the understanding of the pathophysiology of *Malassezia* folliculitis. Thus, this rash has been observed for patients receiving anti-tumor necrosis factor alpha medication (infliximab) for inflammatory bowel disease (231); erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, for renal carcinoma (68); and cetuximab for parotid gland adenocarcinoma (56).

Onychomycoses

Different reports in the literature have linked *Malassezia* yeasts with cases of onychomycoses. However, even in the most well-established cases (57), the question remains whether *Malassezia* has the ability to invade the nail, as no keratinolytic capacity has been demonstrated to date. However, in a case described by Chowdhary et al. (57), the nail invasion of *M. furfur* was proven by histopathology; the pathogenic strain was isolated more than once and was identified by conventional and molecular (sequencing) techniques. In addition, other comorbidities that could affect the nail plate, like psoriasis, were excluded. However, those authors remained skeptical, suggesting that *M. furfur* onychomycosis could have resulted from an initial damage of the nail plate by *Candida albicans*. Reported *Malassezia* onychomycosis case series include those describing laboratory personnel who handled these yeasts (67) and immunocompromised patients (67). In one study, 370 screened patients had a diagnosis of fungal onychomycosis, and a *Malassezia* isolate was involved in 14 cases (289), but in 3 cases, it was coisolated with *Candida albicans* or *Trichophyton rubrum*, which could have been the primary pathogen. Recent cases involved extended hand nail plate damage in a 26-year-old woman (351) and involvement of all hand nails in a 34-year-old male worker (349) and a liver transplant patient (95). Although the therapeutic criterion was stated in the reported cases, the ab-

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sence of a possible pathogenetic mechanism as well as the lack of a constant source of lipids under the nail plate do not support a role for *Malassezia* yeasts, at least as primary pathogens, in onychomycosis.

Malassezia in Systemic Infections

The first report of a systemic infection caused by the alleged "innocent" basidiomycetous yeast *Malassezia* was described in 1979 (327) and complicated the continuous ambulatory peritoneal dialysis of a patient with chronic renal failure. The increased number of immunosuppressed individuals susceptible to rare fungal pathogens (143) append *Malassezia* yeasts as candidate pathogens in adult and neonatal intensive care units (ICUs).

As the majority of cases were reported prior to the implementation of the new taxonomy for *Malassezia* yeasts, the genus name *Malassezia* sp. will be used in order to address cases of lipophilic yeast systemic isolates characterized as *M. furfur* (sensu lato) or *Pityrosporum ovale*, while *M. pachydermatis* will be used for nonobligatory lipophilic isolates.

The majority of published case reports and miniepidemics have involved infants, children, and adults with profound immunosuppression, serious concurrent health problems, and the infusion of total parenteral nutrition (TPN) with lipid supplementation (LS) through central vascular catheters (CVCs). Apart from systemic infections caused by the nonobligatory lipophilic yeast *M. pachydermatis*, the infections caused by the lipophilic *Malassezia* species are divided here into an infant group and into a second group that includes pediatric and adult patients (Table 11).

***M. pachydermatis* infections.** The first case of *M. pachydermatis* infection was described in 1983 in an insulin-dependent diabetic patient on continuous ambulatory peritoneal dialysis who was admitted for weight loss, diarrhea, and cloudy "sterile" peritoneal effluent (103). *M. pachydermatis* was isolated in culture following repeated positive microscopy results for yeast cells in the effluent. The simple removal of the peritoneal catheter and treatment of renal failure with hemodialysis sufficed for cure.

M. pachydermatis was the cause of fungemia in a neonatal ICU, affecting 8 premature (gestational age, 23 to 27 weeks) low-birth-weight (600- to 1,000-g) neonates with multiple comorbidities who received total parenteral nutrition with lipid supplementation (58). *M. pachydermatis* was isolated from blood (6/8 neonates), tracheal aspirate (2/8), eye (1/8) and nose (1/8) secretions, and urine (1/8). The infections were self-limited in 2 neonates, while in the remaining 6 neonates, fungemia was treated with amphotericin B plus flucytosine infusion and fluconazole. The typing of *M. pachydermatis* strains with PCR-random amplification of polymorphic DNA (PCR-RAPD) (Table 8) generated identical profiles, and an exogenous transfer of the *M. pachydermatis* strains was supported. Clonal *M. pachydermatis* and lipophilic *Malassezia* sp. isolates have been serially isolated from incubator surfaces, supporting the suggestion that *M. pachydermatis* strains can persist on incubator surfaces for up to 3 months despite standard cleansing procedures. Thus, meticulous personal hygiene of medical and health care staff handling neonates (52) as well as modifications of the cleansing procedures were implemented (319). The potential transfer of *M. pachydermatis* is highlighted by the fact that DNA has been amplified at high rates from the hands of dog owners regardless of whether the dogs were healthy (92%) or had atopic dermatitis (93%) (225).

Identified risk factors for *M. pachydermatis* systemic infection include an increased median neonatal acute physiology score, >9 days of arterial catheterization, and contact with a potential carrier (52). The presence of intravascular devices and lipid infusion were not identified as risk factors, suggesting that *M. pachydermatis* systemic infections do not share a pathogenetic background identical to that of lipophilic *Malassezia* systemic isolates. The frequency of *M. pachydermatis* systemic infections was determined retrospectively to be 1.6% in the neonatal ICU (191), and *M. pachydermatis* was isolated in that same study from CVCs (4/8 neonates); peripheral blood (2/8); urine (4/8); cerebrospinal fluid (1/8); and eye (1/8), ear (1/8), and tracheobronchial (1/8) discharge. *M. pachydermatis* fungemia in neonates can appear as a cluster of cases (219). In that same study, 28 neonates and 5 adult cases with *M. pachydermatis* infection were additionally retrospectively identified. The screening of specimens for *M. pachydermatis* revealed 44/600 (9%) positive samples, whereas for the adult ICU, *M. pachydermatis* was isolated from only 5 cultures out of 19,000. Eleven lipophilic *Malassezia* strains were also isolated, but no further data were discussed.

The above-mentioned cases, and additional reported data (192, 210), support the role of *M. pachydermatis* as a potential pathogen in the neonatal ICU which is capable of generating small-scale epidemics under favorable circumstances, and the diagnosis should not be overlooked when evaluating symptomatic, low-birth-weight, premature infants receiving total parenteral nutrition with lipid supplementation, as simple removal of the catheter after the identification of the causative agent can lead to clinical improvement.

Lipophilic *Malassezia* species infections. Lipophilic *Malassezia* species infections can be divided in two major groups: the first comprising children and adults with various forms of immunosuppression and diverse clinical syndromes and the second involving infants on parenteral nutrition (Table 11). This discrimination was previously described with insight by Redline et al. in 1985 (262). The diagnosed cases comprised an infant group (3 patients) and a second group with ages ranging from 18 months to 48 years (4 patients). The first group included low-birth-weight premature infants (<12 months of age), while the second group incorporated children (>12 months of age) and adults with serious immunosuppression due to gastrointestinal disease. This classification is followed by the majority of reported cases. All patients reported by Redline et al. (262) were receiving TPN with LS (Intralipid; Pharmacia & Upjohn), and as those authors pointed out, linoleic, oleic, and palmitic acids, which are potent growth stimulants of *Malassezia* species, compose 86% of the TPN-LS infusate. The isolation of the lipophilic *Malassezia* isolate was achieved by use of standard blood culture media (thioglycolate broth and Trypticase soy broth; Bactec), as minimal growth was supported by small amounts of normally contained lipids. The death of 2 out of 3 infants treated with amphotericin B-flucytosine without a discontinuation of parenteral nutrition underscores the importance of alertness in the clinical laboratory for this potential agent of systemic infection. The poor response to amphotericin B (112), is currently supported by the *in vitro*-recorded high MIC values of this agent (320). Recent data showed that the *M. furfur* strains that have the ability to cause systemic infections belong to a distinct internal transcribed spacer 1 group and demonstrate increased phospholipase activity (170).

(i) *Malassezia* species infections in children and adults. The first reported *Malassezia* systemic infection was a case of "sterile

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TABLE 11 Demographic information, clinical and laboratory findings, therapeutic approaches, and outcomes of *Malassezia furfur* (sensu lato) systemic infections and miniepidemics in neonates reported in the English-language literature from 1981 to 2011[a]

Reference	Gender	wt (g)	Gestational age (wk)	Identification procedure(s)	Comorbidity	Age at administration of TPN-LS (days)	Age at infection (days)	Clinical presentation(s)	Therapy	Outcome
7	NR	670	25	Culture	BPD	NR	30	Apnea, bradycardia	Removal of CVC	Favorable
7	NR	900	27	Culture	BPD	NR	90	Asymptomatic	Removal of CVC	Favorable
7	NR	2,910	37	Culture	Cyanotic congenital heart disease	NR	90	Fever, respiratory distress	Removal of CVC	Favorable
7	NR	760	27	Culture	NE	NR	60	Lethargy, atrial thrombus on ultrasound, leucocytosis, thrombocytopenia	Removal of CVC plus treatment with amphotericin B plus fluorocytosine	Favorable
7	NR	1,250	31	Culture	NE	NR	60		Removal of CVC	Favorable
7	NR	3,400	40	Culture	NE	NR	90		Removal of CVC	Favorable
7	NR	1,120	28	Culture	NE	NR	45	Apnea, bradycardia, respiratory distress, leucopenia, thrombocytopenia	Removal of CVC plus amphotericin B treatment	Favorable
17	NR	1,260	NR	Culture	Gastroschisis, NE	11	31	CO, SC	Removal of CVC	Favorable
17	NR	3,000	NR	Culture	Gastroschisis, NE	66	84	CO, SC	Removal of CVC	Favorable
17	NR	620	NR	Culture	BPD	15	58	CO, SC	Removal of CVC	Favorable
17	NR	580	NR	Culture	BPD	18	70	CO, fever, RDS	Removal of CVC	Favorable
17	NR	900	NR	Culture	BPD	19	36	Suspected sepsis	Removal of CVC	Favorable
17	NR	780	NR	Culture	BPD	4	14	CO, SC	Removal of CVC	Favorable
17	NR	1,300	NR	Culture	BPD	4	20	Apnea, bradycardia, suspected sepsis	Removal of CVC	Favorable
17	NR	1,480	NR		Mild BPD	9	25	CO, SC	Removal of CVC	Favorable
17	NR	1,100	NR		Mild BPD	6	30	CO, SC	Removal of CVC	Favorable
17	NR	1,210	NR		Mild BPD	4	24	CO, SC	Removal of CVC	Favorable
17	NR	1,330	NR		Mild BPD	6	20	Suspected NE	Removal of CVC	Favorable
17	NR	1,500	NR		Mild BPD	21	40	CO, SC	Removal of CVC	Favorable
72	F	640	25-26	Culture of blood from Broviac catheter	NE, hyperbilirubinemia, PDA	30	36	Thrombocytopenia	Removal of CVC plus amphotericin B treatment	Favorable
72	M	1,520	32	Culture of blood from Broviac catheter	PDA, apnea of prematurity, meconium plug, NE	36	43	Positive blood culture	Removal of CVC plus amphotericin B treatment	Favorable
72	M	880	26	Culture of blood from Broviac catheter	Recurrent apnea, chronic lung disease, NE	11	53	Thrombocytopenia, leucopenia	Change of umbilical artery catheter	Favorable
72	M	3,345	38	Culture of blood from Broviac catheter	Persistent fetal circulation, hydrocephalus, congenital malformations, *Candida parapsilosis* infection	10	195	Positive blood culture	Discontinuation of TPN with LS plus amphotericin B treatment, temporary sterilization change of catheter 20 days later due to positive *Malassezia* culture	Fatal from *Pseudomonas* sepsis
72	M	1,380	29	Culture of blood from Broviac catheter	NE, colon resection	8	34 (intermittent)	Thrombocytopenia, leucopenia, deterioration of general condition	Discontinuation of TPN with LS plus removal of CVC	Favorable
124	M		40	Blood smear, culture	Hirschsprung disease, bowel resection surgery, multiple catheter-associated bacterial sepsis episodes	7	70	Intermittent fever	Removal of CVC plus amphotericin B treatment	Favorable

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152	NR	<1,500	~24	Culture	BPD	NR	NR	NR	Amphotericin B treatment plus removal of the catheter	Favorable
175	F	NR	34	Buffy coat, culture	Complicated bowel resection	NR	30	Ecchymotic and purpuric lesions, leucopenia, thrombocytopenia	Removal of CVC plus amphotericin B treatment	Favorable
203	F	1,500	34	Buffy coat, culture	NE, bowel resection	14	120	Fever	Removal of CVC plus amphotericin B treatment	Favorable
203	M	2,500	36	Buffy coat, culture	Small bowel volvulus, jejunostomy	~2	75	Fever	Peripheral catheter plus amphotericin B treatment	Favorable
203	F	590	27	Buffy coat, culture	Respiratory failure, neutropenia, thrombocytopenia, gastric perforation, progressive hydrocephalus	~2	50	Apnea, bradycardia, dusky color, lethargy, thrombocytopenia	Removal of CVC plus amphotericin B treatment	Favorable
203	F	1,380	30	Buffy coat, culture	NE, bowel resection	~7	90	Fever	Discontinuation of TPN plus amphotericin B treatment	Favorable
235	M	1,490	30	Gram stain of catheter occlusion precipitate, culture		~7	22	Apnea, bradycardia, catheter occlusion, thrombus formation	Removal of CVC	Favorable
235	F	670	25	Culture	Severe RDS, chronic lung disease	1	28	Precipitate in the catheter, adhesion of catheter	Removal of CVC	Favorable
209	F	NR	NR	Culture	Gastroschisis and postoperative short-gut syndrome	Yes	~180		Miconazole and amphotericin B treatment, removal of CVC	Favorable
209	M	NR	NR	Culture	Gastroschisis and postoperative short-gut syndrome	Yes	~150		Miconazole treatment and removal of CVC	Favorable
251	M	NR	33	Culture		Yes	37	Lethargy, seizures, apnea, bradycardia, hepatosplenomegaly, interstitial pneumonitis, thrombocytopenia	Removal of CVC	Favorable
251	F	NR	27	Culture		Yes	39	Lethargy, apnea, bradycardia, interstitial pneumonitis, thrombocytopenia	Removal of CVC	Favorable
251	F	NR	31	Culture		Yes	46	Apnea, bradycardia, interstitial pneumonitis, thrombocytopenia	Removal of CVC	Favorable
251	M	NR	28	Culture		Yes	70	Apnea, bradycardia, interstitial pneumonitis, thrombocytopenia	Removal of CVC	Favorable
251	F	NR	40	Culture	Chalasia and secondary interstitial pneumonia	Yes	336	Fever, interstitial pneumonitis, thrombocytopenia	Removal of CVC	Favorable

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TABLE 11 (Continued)

Reference	Gender	wt (g)	Gestational age (wk)	Identification procedure(s)	Comorbidity	Age at administration of TPN-LS (days)	Age at infection (days)	Clinical presentation(s)	Therapy	Outcome
252	F	3,100	39	Culture	Gastroschisis, bowel resection, jejunoileal anastomosis, *P. aeruginosa* infection, methicillin-resistant staphylococcal sepsis	38	60	Fever, cardiovascular instability	Removal of CVC	Favorable
261	F	740	28	Pathology	RDS	10	42		Amphotericin B treatment	Fatal
265	M	855 (mean)	25 (mean)	Culture	Hyaline membrane disease				None	Favorable
265	M	855 (mean)	25 (mean)	Pathology	Hyaline membrane disease				None	Fatal
270		567	23	Culture/gram stain of CSF, blood culture	NE, chronic lung disease, intraventricular hemorrhage	1	24 (discontinuation/reinstitution at 62 days)	Hypotension, thrombocytopenia/meningitis	Removal of CVC plus amphotericin treatment	Favorable/fatal
283	M	800	25	Autopsy	PDA			Bilateral pneumonia, severe BPD		Fatal
283	F	710	26	Autopsy	PDA, NE			Fever		Fatal
283	M	765	25	Autopsy	NE, pneumatosis intestinalis, PDA			RDS, feeding problems, bradycardia, intubation, severe BPD, hemorrhage into ventricles of brain		Fatal
291	NR	1,400	31	Culture	Asymptomatic	3	17	No symptoms, colonization	None	Favorable
291	NR	2,500	40	Culture	Cantrell's pentalogy	36	35	Fever, worsening respiratory condition	Discontinuation of TPN plus removal of CVC	Fatal
333	F	1,300	29	Culture		10	49	Fever, lethargy, apnea, bradycardia	Discontinuation of TPN	Favorable
283	M	800	25	Autopsy	PDA, ligation	3	23	Leucocytosis, X-ray-proven pneumonia	None	Fatal
192	F	710	26	Autopsy	PDA, NE, ileum resection	1	64	Hypoxemia, right atrial thrombus	None	Fatal
192	M	765	25	Autopsy	Respiratory distress, NE, pneumatosis intestinalis, PDA ligation	1	58	Leucocytosis, bradycardia	None	Fatal

[a] TPN-LS, total parenteral nutrition with lipid supplementation; BPD, bronchopulmonary dysplasia; NR, not reported; CVC, central venous catheter; NE, necrotizing enterocolitis; CO, catheter occlusion; SC, stable condition; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; M, male; F, female; CSF, cerebrospinal fluid.

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peritonitis," until yeast cells that grew on Sabouraud agar overlaid with olive oil were identified as *Pityrosporum ovale* (327). Lipids leaking postprandially from the small bowel into the peritoneal cavity were incriminated in the overgrowth of this lipophilic yeast. Continuous ambulatory dialysis is an identified risk factor, and subsequent cases have been described (121, 167, 236). The identification of *Malassezia* species as a possible agent of infection can lead to the removal of the catheter and resolution of the infection (236). A common characteristic of systemic infections of *Malassezia* yeasts in adults is the existence of a central venous catheter and total parenteral nutrition (13, 23, 29, 34, 72, 118, 142, 212, 220, 278, 280, 287). Hematologic malignancies (212, 226, 280, 337), cancer (72, 118, 337), and Crohn's disease were the background of *Malassezia* systemic infections. Also, other less common causes include hyperemesis gravidarum (287), quadriplegia (59), preexisting cellulitis, and sinus formation (236). Apart from the symptoms and signs of systemic infection, clinical syndromes that have been attributed to *Malassezia* sp. systemic infections include endocardial mass (278), pneumonia (59, 287), osteomyelitis (337), and meningitis (11). Interestingly, some cases have clustered in the spring and summer months (23), and therapy is always assisted by the prompt removal of the central venous catheter. An alternative therapeutic approach that has been proposed is the "locking" of amphotericin B in the catheter (13).

In conclusion, *Malassezia* sp. systemic infections in adults have variable clinical presentations and can afflict patients with various degrees of immunosuppression. Current data are against their high prevalence, although it is evident that infections caused by this agent, as rare as they may seem, may well be underdiagnosed.

(ii) *Malassezia* species infections in infants. The first report of *Malassezia* fungemia was published in 1981 and described a premature infant (gestational age, 28 weeks; birth weight, 740 g) receiving total parenteral nutrition with lipid supplementation (261). The child developed signs, symptoms, and radiological evidence of pneumonia, with negative bacterial and fungal cultures and without responding to triple-antibacterial chemotherapy. An open-lung biopsy revealed yeast cells, which were erroneously characterized as *Candida* sp. Infusion with amphotericin B plus flucytosine failed to alleviate symptoms and clear the infection, resulting in death on the 66th hospitalization day. An autopsy reported evidence of small-vessel vasculitis with abundant monopolar budding yeast cells, identified as *Malassezia* after morphological study in a mycology laboratory. Since then, a plethora of publications describing *Malassezia* infections in premature and debilitated infants who were receiving total parenteral nutrition with lipid supplementation have been reported (Table 11) (7, 17, 124, 175, 203, 209, 235, 251, 252, 283, 333). As is evident in the cases described in Table 11, the rapid diagnosis and removal of the CVC can suffice for cure when the underlying condition is reversible. An alternative therapeutic approach that has been successfully used incorporates the reallocation of the infusion site to a peripheral vein (209). *Malassezia* sepsis is not very rare, as it was reported for up to 23% of sepsis cases (3 out of 13 patients) (152) in 263 infants prospectively studied in an ICU and in 2/66 (3%) (291) infants after the placement of a central venous catheter. However, as proper isolation media were not used, only 1 out of 102 identified cases of probable fungemia was attributed to *Malassezia* (313). The role of health care personnel in the spreading of *Malassezia* yeasts is significant, as it was incriminated in a miniepidemic during a 7-day period in July 1987 (265). Skin swabs from infants and health care workers revealed that 2 out of 10 infants as well as 2 out of 11 health care workers were colonized. *Malassezia* systemic infections can be controlled when stringent aseptic care of neonates is enforced (152).

An interesting case of *Malassezia* yeast central nervous system infection was described after the spread of intravenous administrated fluid to a ruptured dural vein, which was fatal for the neonate (270).

(iii) Systemic infections by lipophilic *Malassezia* species. *M. sympodialis* is rarely reported to be the causative agent of systemic infection (51, 70, 176). *M. sympodialis* was isolated from the ear lesion of a 53-year-old non-insulin-dependent diabetic man who was receiving intravenous antipseudomonal therapy and was eventually subjected to surgical debridement (51). His condition did not improve but rather deteriorated, with the development of cranial nerve paralysis. Histological examination of tissue specimens obtained from the nasopharynx demonstrated budding yeast cells, and findings suggested a chronic inflammatory reaction. The isolation and identification of *M. sympodialis* with the subsequent administration of intravenous amphotericin B therapy (1 mg/kg of body weight/day) led to a rapid recovery. The patient was subsequently given fluconazole prophylaxis (400 mg once daily) and was free of clinical and radiological signs of infection 6 months later, although the resulting nerve paralysis did not improve. A central venous catheter-associated *M. sympodialis* infection in a 63-year-old man receiving total parenteral nutrition with lipids was reported (176). Identification was pursued by Tween utilization tests (Table 1) and sequencing of the internal transcribed spacer 1 region (Table 2). Unfortunately, that strain was not deposited in an international culture collection; thus, it is not available for further virulence studies. A recent epidemiological study identified *M. sympodialis* catheter colonization in 3 out of 983 intravenous catheters cultured in Dixon's agar (70). In that same study, two more isolates were characterized as being *M. furfur* (sensu stricto), and 2 isolates did not keep in culture long enough to allow identification to the species level. The only clinical information recorded in that study was that the patients were hospitalized in a surgical ward and were not receiving lipid supplementation. More epidemiological surveys accompanied by detailed laboratory studies would substantiate the potential of *M. sympodialis* to cause systemic disease.

Prevention. All observations reported thus far have confirmed the persistence of *Malassezia* yeasts on incubator surfaces and on the hands of health care workers who are pet dog owners. Therefore, the most important preventive measure against the spread of *Malassezia* systemic infection in immunocompromised pediatric and adult patient wards entails the scrupulous adherence of medical and health care staff to standard hygienic measures.

The prevention of *Malassezia* systemic infection by altering the composition of the lipid infusate was suggested by Papavassilis et al. (242). This was based on the observation that medium-chain fatty acids could delay the growth of the seven *Malassezia* species *in vitro*, but as the alteration of the infusate composition raises safety issues, clinical trials to determine both safety and efficacy seem imperative. However, the efficiency of this preventive measure has still not been fully explored.

Conclusion. *Malassezia* isolation followed by identification to the species level should be included in the evaluation of a febrile

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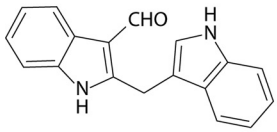
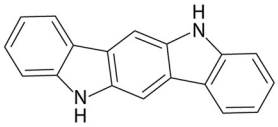
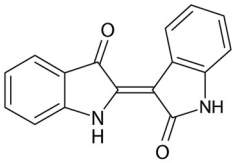


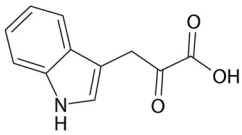
1. Malassezin (336)



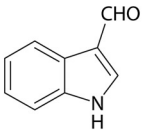
2. Indolo[3,2-b]carbazole (108)



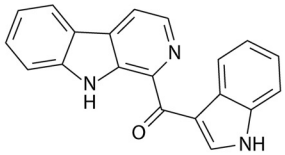
3. Indirubin (120)



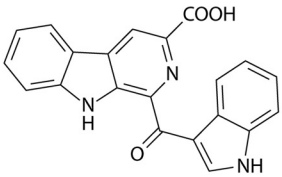
4. (Indol-3-yl)pyruvic acid



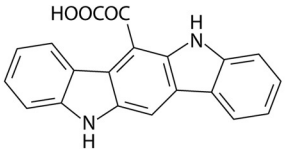
5. Indole-3-carbaldehyde



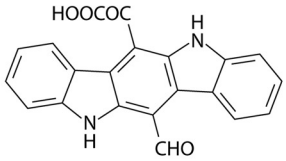
6. Pityriacitrin (215)



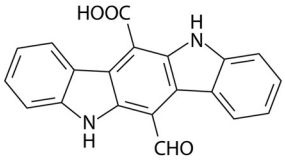
7. Pityriacitrin B (157)



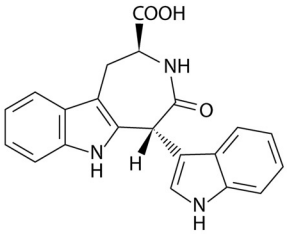
8. Malasseziazole A (158)



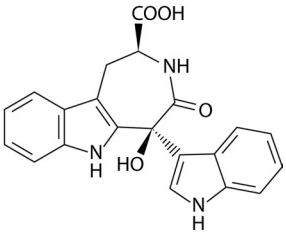
9. Malasseziazole B (158)



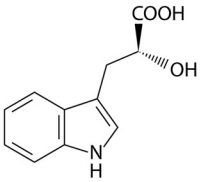
10. Malasseziazole C (158)



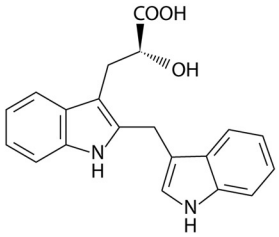
11. Malassezindole A (157)



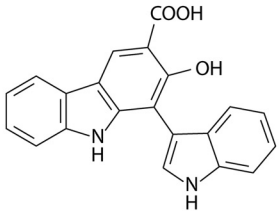
12. Malassezindole B (157)



13. D-indole-3-lactic acid



14. Malassezialactic acid (157)



15. Pityriazole (157)

FIG 7 Chemical structures of the currently identified indoles produced by *M. furfur* when grown on L-tryptophan agar. The corresponding references of the first description of isolation from *Malassezia* extracts are in parentheses.

infant who is receiving total parenteral nutrition with lipid supplementation as well as any patient with immunosuppression and a central venous catheter who presents with persistent fever that is unresponsive to antibiotics and amphotericin B. The seasonal clustering of some reported cases makes this tactic reasonable, especially in ICUs located in countries with a hot and humid climate. Laboratory practices comprising microscopy of blood drawn from the central venous catheter or involved tissue and culture of biological fluids and biopsy specimens in selective medium, as well as an increased incubation time (10 to 15 days), would increase the rate of isolation of lipophilic *Malassezia* species. However, nonspecific laboratory findings that are commonly found in association with *Malassezia* systemic infections are leucocytosis or leucocytopenia and thrombocytopenia.

All reported data confirm that an important aspect of *Malassezia* systemic infections is that they can surface from any back-

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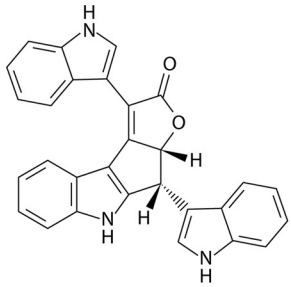
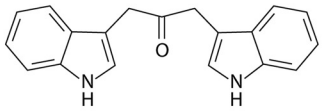
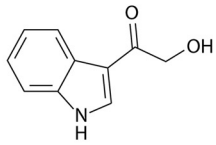


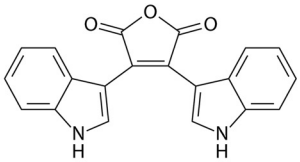
16. Malasseziacitrin (157)



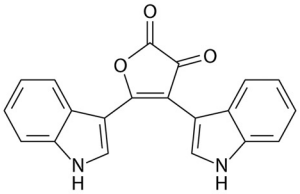
17. Malassezione (157)



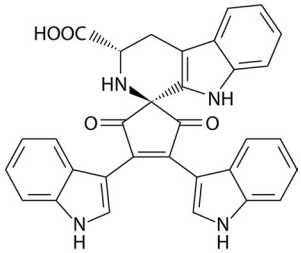
18. 2-hydroxy-1-(1H-indol-3-yl) ethanone (157)



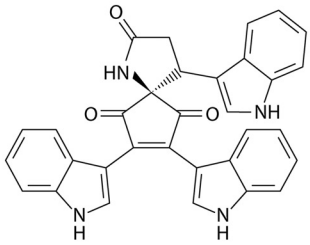
19. Pityrianhydride (157)



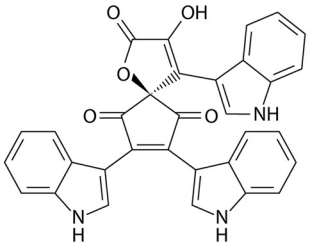
20. Pityrialactone (216)



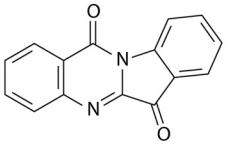
21. Pityriarubine A (158)



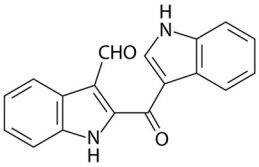
22. Pityriarubine B (158)



23. Pityriarubine C (158)



24. Tryptanthrin



25. Keto-Malassezin (71)

FIG 7 Continued

ground of immunosuppression. Therefore, a high degree of clinical suspicion coupled with laboratory expertise and alertness are prerequisites for the timely management and control of this rare but emerging infection.

Malassezia-Produced AhR Ligands and Significance of AhR Activation on Skin

Malassezia yeasts have the ability to synthesize *in vitro* an array of indolic compounds when tryptophan is used as the single nitrogen source (108, 157, 158, 336). Within these compounds, some of the most potent ligands of the aryl hydrocarbon receptor (AhR) (synonym, dioxin receptor) have been identified, and, as mentioned above, their quantitative production has been linked to *M. furfur* strains isolated from cases of seborrheic dermatitis, dandruff, and pityriasis versicolor. AhR is an orphan nuclear receptor, a member of the *per-arnt-sim* family of proteins, and has pluripotent biological functions in addition to mediating the detrimental effects of dioxin intoxication in the skin and other organs (241). Upon ligand binding, AhR translocates to the nucleus, where it dimerizes with the aryl hydrocarbon nuclear translocator, binds to xenobiotic responsive elements flanking the 5′ ends of genes, and modifies their transcription (155) in a ligand-, cell type-, and tissue-

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specific manner (96, 253). AhR functions in skin physiology by affecting the cell cycle (182, 260) and melanogenesis (204), while it also modifies responses to injuries, as it affects wound healing (155), mediates UV damage (105), and modifies the inflammatory response to immune signals (22, 174). Among the *Malassezia*-produced indoles, indirubin is currently proposed to be the endogenous AhR ligand (1, 253).

Indole derivatives isolated from the genus *Malassezia*. During the last decade, fungi of the genus *Malassezia* and especially those of the species *M. furfur* have been extensively studied for their chemical metabolic profile. When these fungi are cultivated in a selective medium containing tryptophan as the single nitrogen source, they can produce a significant number of chemically diverse indole derivatives (151, 157, 213, 336). A complete list of tryptophan derivatives as *Malassezia* metabolites that have been isolated up to now is shown in Fig. 7.

However, despite the significant number of isolated metabolites, only a few of them have been studied for their biological roles.

(i) Malassezin. Malassezin was initially isolated from ethyl acetate extracts of *M. furfur* cultures (336). It was found that malassezin induces the apoptosis of melanocytes (184). More specifically, a dose-dependent induction of apoptotic markers after the cultivation of melanocytes with malassezin for 24 h was reported. It was also observed that the biosynthesis of melanin is also reduced in a similar dose-dependent way (184). However, the reduction in the level of melanin is most probably due to the apoptosis of melanocytes, and it is not the result of a specific activity on the biosynthetic pathway of melanin. Nevertheless, the characteristic hypopigmentation associated with pityriasis versicolor has been attributed to this biological action of malassezin. Hypopigmentation seems to be enhanced by the inhibition of melanin transportation from melanocytes to keratinocytes due to the breakdown of the actin cytoskeleton (184).

Additionally, malassezin is an AhR agonist with a 50% effective concentration of (EC_{50}) of 1.57 μM, which is able to induce the activity of CYP1A1-dependent 7-deoxyresorufin-O-dealkylase (EROD) in hepatocytes (184). However, malassezin does not fulfill the basic structural characteristics that are necessary for AhR agonist activity (336), and for this reason, it is possible that this type of activity could be attributed to the intracellular transformation of malassezin to indolo[3,2-b]carbazole (ICZ) (108, 184).

(ii) ICZ. ICZ is known as a product of indole-3-carbinol (I3C) condensation in the acidic stomach environment after the ingestion of plants belonging to the genus *Brassica* (*Cruciferae*), such as cabbage and broccoli, etc. (248). I3C is a product of glucobrassicin catabolism, a natural ingredient of the above-mentioned foods (188, 336).

ICZ is a highly active agonist of AhR ($EC_{50} = 2.6 \times 10^{-7}$ M) (108). It is considered one of the most active, nonhalogenated inducers of AhR ever reported *in vitro* (248, 330). The affinity of ICZ for AhR is similar to that of dioxin, while it has been found to regulate the expression of AhR-dependent genes in a way similar to that of dioxin (81).

However, in contrast to dioxin, ICZ is metabolically labile, and for this reason, the effects of ICZ are very different from those of dioxin (54). More specifically, experiments with animals have shown that the administration of one dose or repeated doses cannot affect significantly the food intake of experimental animals, in contrast to dioxin. Moreover, after ICZ administration, no growth inhibition or weight reduction was observed, unlike dioxin. Those same studies showed an induction of CYP1A1 in liver (with an increase in levels of mRNA as well as EROD) in animals receiving 127 μg/kg ICZ for 4 days but not as strong as that achieved by dioxin at 5 μg/kg. The induction of CYP1A1 by ICZ is dose dependent, and in contrast to dioxin, the induction is transient due to ICZ metabolism (54).

In addition to CYP1A1, ICZ also affects another protein, breast cancer resistance protein (BCRP), probably through AhR activation. Experiments with Caco-2 cells have shown that ICZ (2.5 μM) can increase significantly the mRNA expression level of BCRP after 8 or 24 h (90). Furthermore, ICZ presented antiestrogenic activity in MCF-7 cells (201).

(iii) Indirubin. Indirubin and its analogues exhibit inhibitory activities against cell proliferation as well as cytotoxicity and apoptosis induction in human cancer cell lines, and its identification in *M. furfur* extracts (120) expands the spectrum of the interactions of this yeast with the skin. The interest in indirubin and its derivatives has increased significantly in the last years, after the discovery of its inhibitory activity against cyclin-dependent kinases (CDKs) and glycogen synthase kinase 3 (GSK3). Additionally, indirubin has been found to be one of the most active agonists of the AhR and was also proposed to be the natural ligand of this receptor. In order to clarify the role of kinase inhibition and AhR activation by indirubin in cell proliferation, a study of synthetic derivatives with selective activity proved that AhR activation is responsible for the observed cytostatic effects, while the inhibition of CDKs or GSK3 is responsible for its cytotoxicity (182).

(iv) Pityriacitrin. Pityriacitrin acts as a strong UV absorbent and most probably is produced by fungal cells as an agent that protects against UV light (206, 215). The presence of pityriacitrin on human skin was initially proposed to convey UV protection to the hypopigmented lesions of pityriasis versicolor and prevent skin from the development of sunburn (190). However, those results were not confirmed by subsequent *in vitro* experiments (116), and the substances produced by *Malassezia* yeasts that protect against UV *in vivo* are still under investigation.

(v) Pityrialactone. Pityrialactone is also an agent that protects against UV, like pityriacitrin. It is a compound presenting intense yellow-green fluorescence. Its presence in the skin would probably explain the fluorescence observed for pityriasis versicolor skin under Wood lamp fluorescence (216).

(vi) Pityriarubins. Pityriarubins are bis-indol derivatives with unique structures (158) showing inhibitory activity against the oxidative burst of human granulocytes. Their presence *in vivo* could explain the absence of inflammation in diseased skin.

(vii) Tryptanthrin. Tryptanthrin is an alkaloid found in a number of plants, most of them also producing indigo and indirubin. It is a potent inhibitor of prostaglandin and leukotriene synthases in various cell lines and a selective inhibitor of cyclooxygenase 2 (COX-2) (73) and of inducible nitric oxide synthase (iNOS) (NOS II) expression (162). It inhibits the production of IFN-γ and IL-2 after the stimulation of Peyer's patch lymphocytes with staphylococcal enterotoxin B (SEB) (309). Tryptanthrin was also found to inhibit P-glycoprotein (Pgp) through MDR1 gene suppression (346). It was also reported to act as a moderate AhR inducer (281).

(viii) Malassezindole A and keto-malassezin. Malassezindole A has shown activity in the inhibition of tyrosinase (71) and probably can affect melanin synthesis. Keto-malassezin is also probably

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a tyrosinase inhibitor capable of inhibiting the dopa reaction on human epidermal melanocytes (71).

Synergy-preferential biosynthesis. It seems that the synergy between the indole derivatives found in *Malassezia* can explain some of the clinical symptoms of pityriasis versicolor, like depigmentation (malassezin), resistance to UV light, and reduced inflammatory reactions (pityriarubins) (151, 183).

It should be noted that a number of indole derivatives, like malassezin, ICZ, and indirubin, have been found to be preferentially synthesized by *M. furfur* strains isolated from seborrheic dermatitis lesions. These compounds are synthesized in significantly higher numbers by strains isolated from diseased skin than by strains isolated from healthy skin (108, 120). These compounds are among the most active known AhR agonists, and this common property implies the possible role of this receptor in the development of *Malassezia*-related skin diseases.

***Malassezia* and future research perspectives on skin cancer.** The production of the above-mentioned array of AhR ligands by *Malassezia* raises the question of a possible participation of this yeast in skin carcinogenesis through the activation of this receptor. Current evidence points toward an association of these yeasts with basal cell carcinoma (115), the malignant tumor with the highest incidence in Caucasians worldwide. Presently, solar UV light is regarded as the most significant carcinogen for this tumor; however, not all basal cell carcinomas are caused by UV light, as these tumors are rare in certain anatomical areas subjected to intense UV radiation exposure throughout life (i.e., dorsal aspects of the hands) and commonly appear on relatively sun-protected skin localizations (i.e., eyelid, inner canthus, and retroauricular area) (145). In the pathogenesis of basal cell carcinomas, activating mutations of the hedgehog pathway at the cellular level are implicated (94, 154), while at the tissue level, they act together with the induction of immune tolerance by the establishing tumor (immunosubversion) (172, 178, 352). The latter is a well-recognized common process in the progression of many types of cancer. Epidemiological observations that indirectly link *Malassezia* to basal cell carcinoma have come from studies of patients with Parkinson's disease, for whom seborrheic dermatitis and basal cell carcinoma appear at higher rates than expected by a random association despite the reduced prevalence of most other malignancies in this group of patients (102). Additional epidemiological data from different animal species on the rate of *Malassezia* colonization implied a role for this yeast in the induction of this type of cancer. *Malassezia* yeasts and basal cell carcinoma are more common in dogs and cats (33), while they are extremely rare in lagomorphs and rodents (325). In dogs and cats, these tumors develop on the head and neck region (272), overlapping with the *Malassezia* niche in these animals. Furthermore, in dogs, these tumors are more common in hairy animal breeds with long pendulous ears (Saint Bernards and Scottish Terriers), an anatomical trait that promotes *Malassezia* overgrowth (115). Furthermore, in humans and animals, these tumors and *Malassezia* yeasts accrue in the so-called seborrheic areas of the face and trunk. Basal cell carcinoma promotion by the *Malassezia*-synthesized AhR ligands could happen through a modification of UV radiation-induced carcinogenesis, favoring a shift toward the salvage/survival of initiated tumor cells, the inhibition of cell senescence, alterations in vitamin D metabolism, the induction of immune tolerance, and, finally, the procarcinogenic modulation of cell cycle progression and apoptosis (115).

ACKNOWLEDGMENT

The International Society for Human and Animal Mycology (ISHAM) *Malassezia* working group continues to promote multidisciplinary global collaborative research.

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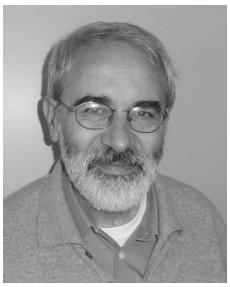

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