Malassezia virulence factors and their role in dermatological disorders

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Abstract

Malassezia is a commensal fungus that constitutes normal skin microbiota. However, in certain conditions and individuals, it may transform into a pathogenic yeast with multiple associated dermatological disorders and various clinical manifestations. This phenomenon is influenced by a unique host–agent interaction that triggers the production of several virulence factors, such as indoles, reactive oxygen species, azelaic acid, hyphae formation, and biofilm formation. This review article discusses *Malassezia* virulence factors that contribute to the transformation of *Malassezia* from commensal to pathogenic as well as their role in dermatological disorders, including pityriasis versicolor, seborrheic dermatitis, *Malassezia* folliculitis, atopic dermatitis, and psoriasis.

Keywords: atopic dermatitis, *Malassezia*, pityriasis versicolor, psoriasis, seborrheic dermatitis, virulence factors

Introduction

Malassezia is a lipophilic and lipid-dependent commensal fungus that, along with other microorganisms, constitutes the normal skin microbiota (1). It is included in the phylum *Basidiomycota*, subphylum *Ustilaginomycotina*, class *Malasseziomycetes*, order *Malasseziales*, and family *Malasseziaceae* (2). To date, 18 species have been isolated from healthy and lesional skin of humans and animals. *Malassezia* has a small genome size, with only 4,285 genes and a size of 9 Mb (3). This small size may reflect the fungus's adaptation to its limited habitat, which is on the skin of warm-blooded vertebrates (4).

Different species of *Malassezia* may lead to distinct clinical manifestations, ranging from hypopigmented macules without visible inflammation to eczematous findings with desquamation and inflammation. Out of all diseases, despite still being controversial, *Malassezia* is widely regarded as a pathogenic agent in pityriasis versicolor and *Malassezia* folliculitis. The finding of *Malassezia* in the seborrheic area still requires confirmation of its pathogenic role because its commensal status is still difficult to distinguish from its pathogenic phase (4). The evidence for the role of *Malassezia* in psoriasis and atopic dermatitis (AD) is less robust (5).

As a commensal fungus, *Malassezia* may shift to being pathogenic. The majority of *Malassezia* pathogenic potentials is determined by the activation of various lipase enzymes. The effectiveness of utilizing nutrients available on the skin surface and sebaceous glands, in addition to determining the size of the *Malassezia* population, is also essential in determining the quality and quantity of the byproduct metabolites produced. These metabolites range from irritative fatty acids to bioactive indole derivatives that lead to regulation of downstream metabolic pathway expression (6).

This review article discusses *Malassezia* virulence factors that contribute to the transformation of *Malassezia* from commensal to pathogenic and their role in several dermatological disorders, such as pityriasis versicolor, seborrheic dermatitis, AD, and psoriasis.

Malassezia spp. virulence factors

Extracellular lipase

Malassezia is a lipid-dependent microorganism because it lacks the genetic codes required for synthesizing myristic acid, a precursor of long-chain fatty acids (6). *Malassezia* compensates for this by coding hydrolase enzymes such as lipase and phospholipase (6, 7). A study by Juntachai et al. revealed that all *Malassezia* species show high lipase activity, with the highest shown by *Malassezia globosa* (7). Real-time polymerase chain reaction (RT-PCR) showed that *M. globosa* produces 14 lipase enzymes, 12 of which can be further classified into two Pfam (protein family) groups: LIP and lipase 3 (8). The hydrolysis capability of these enzymes results in fatty acids that integrate with the *Malassezia* cell membrane, which not only support its growth but also enhance its pathogenicity (9). The high lipid content of the *Malassezia* cell membrane contributes to increasing the resistance of *Malassezia*, hyphae mechanical stability, and increased osmoresistance (6, 10). In addition, this composition protects *Malassezia* from phagocytosis and debilitates the host immune response (6).

Indoles

Malassezia yeasts convert tryptophan into alkaloid indoles such as malassezin, indirubin, and indolo [3,2-b] carbazole (ICZ). These indoles are potent aryl hydrocarbon receptor (AhR) ligands and therefore may modify the response of all cells expressing AhR, such as inducing melanocyte apoptosis and inhibiting neutrophil activity (11, 12). Thus, as is further discussed below, indoles are associated with an impaired immune system and characteristic skin lesions associated with *Malassezia* infection.

Reactive oxygen species

Malassezia yeasts produce reactive oxygen species (ROS), which are hypothesized to play a significant role in the pathogenesis of seborrheic dermatitis and pityriasis versicolor. Six *Malassezia*

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species—*M. furfur*, *M. globosa*, *M. sympodialis*, *M. slooffiae*, *M. obtusa*, and *M. panchydermatis*—are reported to produce ROS (13). A study also showed that clinical improvement was associated with a decline in ROS level (14). ROS induce cell destruction through its cytotoxic effect, which is mediated by lipid peroxidase and the oxidation of enzymes and proteins (13).

Lipooxygenase

Lesional skin of patients with pityriasis versicolor expressed a higher lipoxygenase level compared to non-lesional skin (6, 15). Lipoxygenase level increases with an increase in unsaturated fatty acid level; oxidation of unsaturated fatty acids by lipoxygenase produces dicarboxylic acid, a competitive inhibitor of tyrosinase (16). It is also a dioxygenase enzyme that catalyzes the formation of hydrogen peroxide from unsaturated fatty acids such as linoleic and arachidonic acid, which consequently affects physiological functions such as inflammation, skin barrier disorders, and tumorigenesis (17). Some antifungal agents, such as itraconazole, ketoconazole, and terbinafine, convey their anti-inflammation property by inhibiting metabolite formation of lipoxygenase (18).

Azelaic acid

Azelaic acid is a compound produced by *Malassezia* when cultured in a medium containing olive oil. This compound is a dicarboxylic acid group that, as mentioned above, inhibits tyrosinase and hence leads to depigmentation (19). Azelaic acid is also associated with a reduction in OH·, O_2-, and H_2O_2 levels, the factors needed in oxidative mechanisms required in phagocytosis, which might explain why phagocytosis is ineffective in *Malassezia*, with only 5% being able to be phagocytosed after 2 hours (20).

Melanin

The virulence of various types of fungi has been shown to be associated with melanin. Its negative charge and hydrophobicity transform the charge of the fungal cell surface and inhibit phagocytosis. In addition, melanin decreases nitric oxide production, which consequently decreases the host oxidative capability (21). Youngchim et al. showed that *Malassezia* produced melanin when reacting with L-3,4-dihydroxyphenylalanine (L-DOPA), a phenolic compound (22).

Hyphae formation

Hyphae are an important virulence factor because *Malassezia* infection is initiated by the transformation of yeast to hyphae form (22, 23). A study showed that *Malassezia furfur* transforms into hyphae following the addition of L-DOPA, a diphenolic compound that is oxidized into a quinolone (diphenolase activity) and kojic acid in lipid-containing medium (22). This suggests that L-DOPA is essential in *Malassezia* hyphae formation.

Cell surface hydrophobicity, adherence, and immune response stimulation

Cell surface hydrophobicity (CSH) plays an important role in the pathogenicity of multiple microorganisms (24–27). CSH in fungi has been more extensively studied, and hence is better understood in *Candida* spp. (28, 29); however, studies in recent years

have suggested that CSH is also expressed by *Malassezia* spp. and may play a role in its pathogenicity.

Akaza et al. examined the CSH of five *Malassezia* species—*M. furfur*, *M. sympodialis*, *M. dermatis*, *M. globosa*, and *M. restricta*—through the microsphere assay method. In this study, 100 μl of yeast cells was mixed with 10 μl of microsphere suspension and was examined under the microscope. It was found that all isolates expressed CSH with the highest shown by *M. furfur*, with a rate of more than 50% (27). Angiolella et al. presented a similar finding, in which 14 out of 16 strains of *M. furfur* showed medium-high CSH (39.4 to 83.25%) (26).

This hydrophobicity also affects how *Malassezia* adheres to host cells (30, 31). Adherence is often regarded as the first important step in fungal infection and is a major virulence factor in the pathogenesis of fungal infection (31). The study by Angiolella et al. also showed that all 16 strains expressed high adherence ability, ranging from 29.2 to 78.7% (26). Adherence is important in inducing keratinocytes to produce pro-inflammatory cytokines. Akaza et al. examined the mRNA expression of normal human epidermal keratinocytes (NHEK) cultured with *Malassezia* of various species; compared to NHEK unexposed to *Malassezia*, the exposed group showed a significantly higher expression of interleukin (IL)-1α, IL-6, and IL-8 mRNA, with *M. furfur* showing the highest proinflammatory cytokine expression (27). However, this expression might be subject to certain factors, such as culture condition and medium. Further studies are needed to confirm this finding.

Biofilm formation

Biofilm is an immobile microbial community that strongly adheres to each other and to the cell surface, which is protected by an extracellular matrix composed of polysaccharides. These cells have phenotypes distinct from planktonic cells and are associated with resistance to infection (32). Biofilm formation has been more extensively studied in bacteria (33–35). Most studies of fungal infection have only examined *Candida* spp. (36, 37); data on biofilm formation in *Malassezia* are still limited, but more studies are being carried out.

To date, no *Malassezia* biofilm formation model has been proposed. The only detailed description is only available for biofilm formation by filamentous fungi (38). This process is initiated by phase I, the adsorption phase, which occurs when spores, a hyphal fragment, or sporangia contact the surface. This is followed by phase II, the active adhesion phase, in which spores release adhesin during germination or other reproductive processes, including microcolony formation. Phase III includes hyphal elongation and branching to form a monolayer with extracellular matrix production. The second microcolony formation or initial maturation occurs in phase IV, in which a dense hyphae network forms a three-dimensional structure covered by an extracellular matrix and water channel formation. Complete biofilm formation can be observed in phase V, and it ends with dispersion or the planktonic phase (phase VI), in which conidia and/or a hyphal fragment is released to start a new cycle (32, 38). An interesting phenomenon observed is the secretion of small proteins called hydrophobins, which play a role in adhesion to a hydrophobic surface and may be crucial in biofilm formation (32).

Although the exact biofilm formation by *Malassezia* is not clearly delineated yet, a study showed that adherence and hydrophobicity play important roles (26). Out of 17 *M. furfur* strains,

Angiolella et al. showed that all isolates were able to form biofilm after 48 hours, with eight and five isolates showing high and medium biofilm production, respectively (26). Furthermore, it is interesting to observe that 63% of isolates with high biofilm formation also showed medium to high hydrophobicity and/or adherence, and all strains with medium biofilm production showed medium hydrophobicity and adherence. A similar result was suggested by Bumoroongthai et al., who showed that maximum biofilm formation occurred after 72 hours, with a higher biofilm level found in mixed isolates compared to a single isolate (39).

Biofilm formation is associated with decreased susceptibility to antifungal agents. The minimum inhibitory concentration of biofilm-forming cells is significantly higher compared to planktonic cells (> 16 μg/ml vs. < 0.03 μg/ml, $p < 0.0001$). This resistance is mediated by the barrier effect of the extracellular matrix (40). The barrier contains a high concentration of protein, phosphorus, and carbohydrates, which may sequester and consequently dampen the effect of antifungal agents (41).

The association between *Malassezia* virulence factors and dermatological disorders

The pathophysiology of dermatological disorders associated with *Malassezia* is still mostly unclear. In healthy skin, *Malassezia* utilizes the available nutrients for growth without causing any disease to the skin. A disturbance in this physiological interaction will cause *Malassezia* yeast to adapt and modify the expression of enzymes that are involved in energy acquisition, such as lipase and phospholipase (42), and at the same time synthesize bioactive indoles that promote their effect through the AhR, which is expressed on the surface of almost all epidermal cells (43).

Figure 1 shows the interaction between *Malassezia* yeasts and skin. The yeasts acquire nutrient and sebum lipid to form their outer surface and amino acids to synthesize melanin and AhR indolic ligand. In addition, they are also able to modify the excretion of lipase and phospholipase under the influence of β-endorphin. Cellular components (enzymes, proteins, glyceroglycolipids, and mannosyl fatty acids) induce the host innate and adaptive immune system. AhR ligand may down-regulate the immune response, modify epidermal cell function, interfere with AhR-UV-induced damage and melanogenesis, and potentially inhibit antagonist microbes (42).

The ultimate challenge is to delineate a comprehensive understanding of the highly varied interactions between *Malassezia* yeast and the skin in normal and pathologic conditions such as a) commensalism (as observed in normal skin) because there is no evidence of a mutualistic relationship between *Malassezia* and skin, b) alteration in melanocyte function that leads to hypo- or hyperpigmentation without visible inflammation (pityriasis versicolor), c) inflammation without evidence of a significant adaptive immunity response (seborrheic dermatitis and dandruff), and d) induction of specific immunity (AD) (42).

Pityriasis versicolor

In addition to the consistent finding of *Malassezia* yeast from pityriasis versicolor lesions, there are two facts that further support the role of *Malassezia* in this disease: (i) a positive culture is more frequently encountered in specimens grown from lesional skin than from healthy skin (44), and (ii) a hyphal form is consistently observed in samples taken from pityriasis versicolor lesions, independent of the *Malassezia* species isolated (5).

It is interesting to observe that, despite the high fungal load in lesional skin, no visible inflammatory response is observed. This finding might be attributed to the production of indoles by *Malassezia*, especially *M. furfur*, which are able to down-regulate the inflammatory cascade. Indoles such as pityriarubin inhibit neutrophil release whereas indirubin (45) and ICZ inhibit dendritic cell maturation (12). In addition, *Malassezia* spp. also produces malassezin, which may stimulate melanocyte apoptosis. Other metabolites produced by *Malassezia*, especially *M. furfur*, are shown in Table 1 (46).

Table 1 | *Malassezia furfur* **metabolites (43).**

Metabolite	Effect
Azelaic acid	Tyrosinase inhibition
Malassezin	AhR agonist that induces melanocyte apoptosis
Pityriacitrin	Absorbs ultraviolet
Pityrialactone	Alkaloid indole that fluoresces under 366 nm wavelength
Pityriarubin	Inhibits neutrophil release and 5-lipooksigenase activity

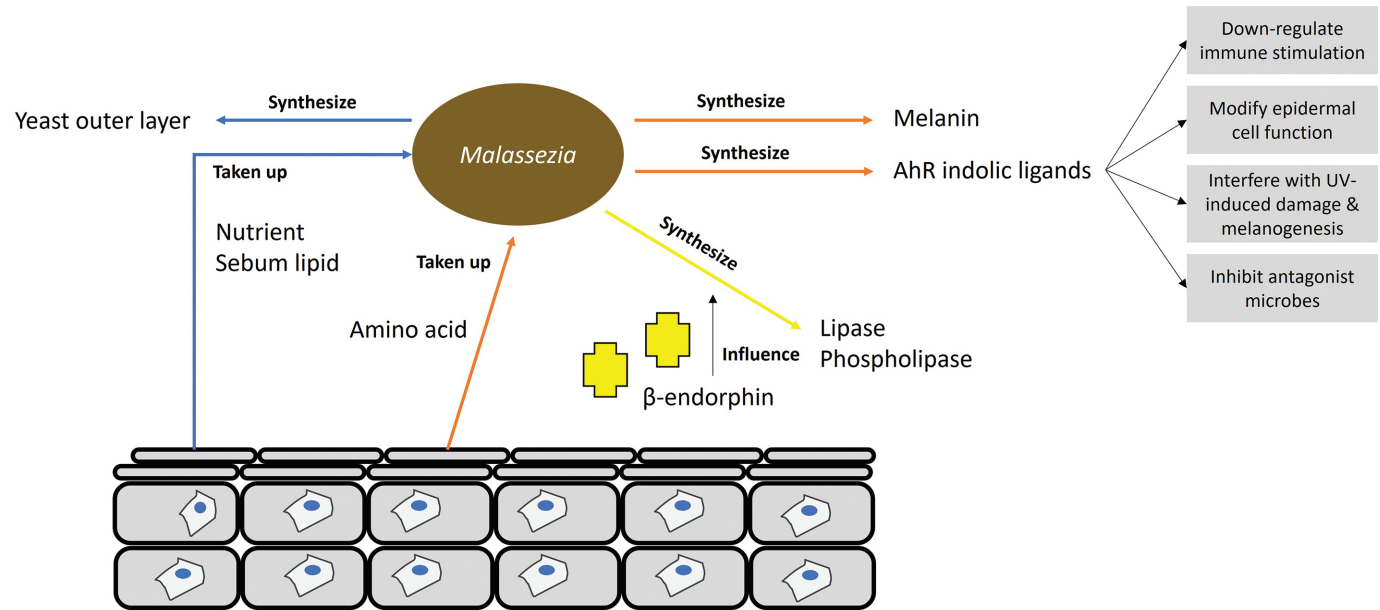AhR = aryl hydrocarbon receptor.

Figure 1 | *Malassezia* interaction with the skin. AhR = aryl hydrocarbon receptor, UV = ultraviolet.

Thus, the combination of anti-inflammatory effect and various hypopigmentation mechanisms results in a characteristic clinical manifestation: hypopigmented macules without a dominant inflammatory condition.

Seborrheic dermatitis

The putative relationship between *Malassezia* and seborrheic dermatitis was first described by Louis-Charles Malassez in 1874. Shuster supported this finding by showing that antifungal administration resulted in clinical improvement of seborrheic dermatitis (47). The improvement of molecular diagnostic technology shows that *M. globosa* and *M. restricta* are two of the most frequently isolated *Malassezia* species (5, 47).

Malassezia is mainly found in the sebaceous gland infundibulum, where lipids, the main energy source for *Malassezia*, are abundant. Because this microorganism is usually commensal, the mechanism that triggers seborrheic dermatitis is still unclear (47). *Malassezia* produces lipase, which hydrolyzes sebum triglyceride and releases unsaturated fatty acids such as oleic acid and arachidonic acid (48). These compounds disrupt keratinocyte differentiation, which leads to stratum corneum abnormalities such as parakeratosis, intracellular lipid droplet, and irregular corneocyte sheath. These metabolites also induce keratinocyte production of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, interferon gamma (IFN-y), and tumor necrosis factor α (TNF-α), consequently perpetuating inflammation. In addition, arachidonic acid acts as a source for prostaglandin, a pro-inflammatory mediator, which stimulates inflammation through neutrophil recruitment and vasodilation (48, 49).

Although the above data support the pathogenic role of *Malassezia* in seborrheic dermatitis, there is robust evidence that shows that individual predisposition and host–*Malassezia* interaction, in addition to the mere presence of *Malassezia*, are essential in seborrheic dermatitis. Moreover, because *Malassezia* is also found on healthy individuals, topical application of oleic acid does not induce a significant clinical change in healthy individuals, but it is able to induce desquamation on non-lesional skin of seborrheic dermatitis patients. This finding is suggestive of the role of an epidermal barrier intrinsic defect in seborrheic dermatitis pathogenesis (48, 50).

Current data are still insufficient to define *Malassezia* virulence factors that are responsible in the development or exacerbation of seborrheic dermatitis. Because skin is the niche for *Malassezia*, a unique interaction between this yeast, keratinocytes, and immune cells determines the transformation of this commensal yeast to pathogenic (5).

Environmental factors such as UV radiation and antagonistic microorganisms may induce physiologic stress on *Malassezia* and the skin. Thus, the ability of *Malassezia* to modify the immune system, in addition to individual susceptibility and yeast metabolite production, may play a central role in triggering and perpetuating inflammation in seborrheic dermatitis. Isolates taken from seborrheic dermatitis lesions show higher AhR production compared to healthy skin (43).

Malassezia folliculitis

As its name suggests, *Malassezia* folliculitis refers to infection of the pilosebaceous unit by *Malassezia* yeasts (51). Clinically, it presents as monomorphic, erythematous pruritic papules and/ or pustules on seborrheic areas, mainly on the trunk (chest and back) and to a lesser extent on the upper arms, neck, and face (52, 53). Gram staining using KOH from specimens taken from pustules reveals unipolar budding yeast (51) that were both sensitive (84.6%) and specific (100%) (53). Histopathological examination has revealed follicular dilatation and a high number of *Malassezia* conidia; hyphae are rarely found (54).

Diagnosis of *Malassezia* folliculitis can be established when two of the following three criteria are met: typical clinical presentation, a biopsy showing *Malassezia* in the inflamed hair follicle, and a response to antifungal therapy (53).

Atopic dermatitis

AD is characterized by an epidermal barrier function defect, increased transepidermal water loss, increased surface pH, decreased stratum corneum hydration, and down regulation of tight junction component expression (55). As mentioned above, *Malassezia* spp. is a part of normal skin microbiota and constantly interacts with the immune system of the skin, such that IgG and IgM against *Malassezia* can be found in normal healthy individuals (4). However, healthy individuals (non-atopic) are not sensitized by *Malassezia*, whereas there is a high proportion of atopic individuals that are sensitized to this yeast, which is possibly caused by an allergen produced by *Malassezia* (56). The underlying mechanism of this phenomenon is still unclear; however, this might result from the interaction between a skin barrier defect, a genetic factor, and an environmental factor (57). The production of phospholipase may also further down regulate the lipid level in atopic individuals whose skin lipid level has already declined.

The increased pH in AD patients triggers allergen release by *Malassezia*, which, together with *Malassezia* cells, penetrate the epidermis through the already disrupted epidermal barrier. *Malassezia* and the allergen are then recognized by toll-like receptor 2 expressed by keratinocytes and dendritic cells, which results in the release of pro-inflammatory cytokines such as IL-1, IL-4, IL-5, IL-6, CXCL-8, IL-12p40, and IL-13. Components of *Malassezia* also induce B cells to produce *Malassezia*-specific IgE, which is activated by dendritic and T-cells. IgE, possibly produced by mast cells, also plays a role in the inflammation that occurs in AD patients. Moreover, autoreactive T-cells can cross-react with fungal and human manganese-dependent superoxide dismutase (MgSOD), hence perpetuating inflammation (57).

The clinical advantage of adding antifungal agents to standard AD treatment regimen seems to be promising only in certain subsets of AD patients. Combining antifungal agents, topical or systemic, and corticosteroids seems to be effective for those experiencing head and neck AD and for those with detectable *Malassezia*-specific IgE (58). Azoles are typically the antifungal of choice because they also confer anti-inflammatory properties (59).

Psoriasis

The possible role of *Malassezia* in psoriasis was first identified in 1873 by Rivolta, who isolated *Malassezia* from a psoriatic lesion. However, epidemiological data on the distribution of *Malassezia* in psoriatic lesions is still inconsistent (60). To date, the pathophysiology of psoriasis is mainly attributed to a complex formed by self-DNA released by keratinocytes and cathelicidin antimicrobial peptide LL-37, which stimulates plasmacytoid dendritic cells to produce IFN-α. This process initiates and perpetuates psoriasis

lesions. The increase of LL-37 may decrease the *Malassezia* population or instead may occur secondary to *Malassezia* invasion of the skin (60). A study showed that the rate of positive culture is higher in psoriasis patients than in normal subjects, with *M. globosa* being the most frequently isolated species. In addition, *M. globosa* in the form of yeast and pseudohyphae was also the most frequently isolated species during psoriasis exacerbation (61). Furthermore, T-cells reactive to *Malassezia* yeast (62) and antibodies against *Malassezia* (63) have been found in lesional skin but not in normal subjects. Further studies are still needed to clarify the role of *Malassezia* in psoriasis.

The evidence for the benefit of antifungals in psoriasis is still contradictory. Antifungals may be beneficial in scalp psoriasis resistant to other topical or systemic treatment (64). Although one study supports this notion (65), this is refuted by another trial (66). More placebo-controlled, randomized controlled studies are required to clarify this result.

Conclusions

The shift of *Malassezia* from commensal to pathogenic is associated with its virulent factors. Although the role of *Malassezia* in most dermatological disorders is still unclear, a rising body of evidence has been shown by multiple studies. The mechanism by which *Malassezia* induces different immune responses, and hence different clinical manifestations in different diseases, still needs to be deciphered. This calls for further investigation to clarify the role of *Malassezia* in dermatological disorders and the potential of new treatment approaches.

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