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The Review of the Pathogenic Elements Associated with Malassezia

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Abstract. Malassezia is a yeast that typically exists as a harmless organism within the host's skin flora. However, under specific microenvironmental conditions, it can transform into a pathogenic form directly linked to seborrheic dermatitis and pityriasis versicolor. These findings highlight the critical need to decipher its phase transition mechanisms, particularly the lipase activation threshold triggering pathogenicity. Within this broader analytical framework, this paper reviews what the evidence appears to reveal regarding the pathogenic factors of Malassezia based on what seems to emerge from existing literature and data. What the analysis tends to support is that the relationship between Malassezia and its human host appears to be complex, seemingly varying by body site, age group, and what appears to be host susceptibility. The pathogenicity of Malassezia is not an inherent attribute but rather a dynamic process triggered by imbalances in the host microenvironment. Future research must employ integrated multi-omics approaches (microbiomics, metabolomics, and immunomics) to dissect strain adaptation mechanisms. This will advance precision intervention strategies targeting host-microbe interactions, thereby facilitating a paradigm shift from "antimicrobial" to "microbiome-preserving" therapeutic approaches.

Keywords: Malassezia, Symbiosis, Pathogenesis, Pathogenic Mechanisms, Skin Microbiota, Strategies

1. Introduction

Malassezia is a yeast that commonly resides in the host's skin microbiota as a harmless commensal [1]. These yeasts appear to represent a component of the skin's normal microbiota, seemingly playing a vital role in maintaining the balance of skin ecosystems. However, under specific conditions—such as what tend to be alterations in sebum production, variations in humidity levels, or changes in immune responses—Malassezia can ostensibly proliferate excessively, potentially resulting in various skin disorders. What appears particularly significant about these findings is the shift in Malassezia's behaviour which seems to change from being a harmless part of the skin's natural microbiota to becoming a possible cause of various skin conditions, warranting a thorough explanation. Within this broader analytical framework, Malassezia's transition from "commensalism to pathogenicity" appears to be a dynamic process driven by what tends to suggest tripartite interactions among host, microbe, and environment. The evidence appears to reveal that strain adaptability (e.g., metabolic reprogramming) and host susceptibility collectively determine disease

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phenotypes [2]. In light of these methodological considerations and the complexity of these theoretical relationships, this paper examines the pathogenic elements associated with Malassezia to investigate its pathogenicity and provide directions for future research on targeted drugs and treatment methods. The current core therapies rely on topical antifungals (e.g., ketoconazole) and oral itraconazole. However, limitations such as inadequate skin penetration, biofilm barriers, and host immune defects result in recurrence rates exceeding 50%. Combination therapy (e.g., antifungal + anti-sebum agent spironolactone + immunomodulators) significantly enhances efficacy (reducing 1-year recurrence to 13.8%). Meanwhile, natural components (e.g., cinnamaldehyde) and microecological agents (e.g., Paenibacillus polysaccharides) demonstrate potential by inhibiting virulence factors and repairing skin barriers. Strategies include developing nanocarrier delivery systems (e.g., lipid-encapsulated drugs) to enhance penetration efficiency and combining them with natural extracts to block lipase pathogenic pathways. Additionally, designing personalized probiotic transplants or functional polysaccharides can help reconstruct microbial homeostasis based on the 'fungi-bacteria-host' interaction network.

2. Malassezia characteristics

Malassezia yeast can transform into a pathogenic organism under certain conditions, such as increased temperature, humidity, greasy skin, sweating, and immunosuppression. In addition, one study found that these changes are associated with the composition of fatty acids in the sebaceous gland due to an increase in androgen concentration [1]. Microbial density is positively correlated with sebaceous gland activity, with peak levels observed from adolescence to early adulthood (11-30 years).

2.1. Morphological characteristics

Malassezia spp. are obligate lipid-dependent yeasts with oval budding cells, monopolar reproduction, prominent lipid droplets, and yeast-hyphal dimorphism that enhances pathogenicity. Malassezia exhibits oval or spherical unicellular morphology (diameter: 2–8 μm), reproducing through multilateral budding without forming pseudohyphae (unlike Candida spp.). The cell wall consists of a β-glucan/chitin scaffold layered with hydrophobic glycoproteins (e.g., Mp65), facilitating cutaneous adhesion and immune evasion. Critically, the absence of fatty acid synthase genes (e.g., FAS2) renders it lipid-dependent, necessitating assimilation of host sebum-derived long-chain fatty acids (C11–C24) for synthesizing membrane phospholipids.

2.2. Physiological characteristics

Malassezia species are obligatorily lipid-dependent yeasts characterized by unique physiological traits, including the inability to synthesize fatty acids de novo and consequent reliance on host sebum lipids for growth. Their key metabolic features encompass potent lipase-mediated hydrolysis of triglycerides into free fatty acids, β-oxidation of C11-C24 carbon chains, and thermo- and pH-dependent dimorphism (yeast-hyphal switching at 37°C/pH 5.0–6.0). These fungi exhibit microaerophilic preferences with optimal growth under low oxygen tension, express temperature-dependent virulence factors (e.g., phospholipase C and indole derivatives), and notably form drug-resistant biofilms through extracellular matrix production, ultimately contributing to their pathogenesis in dermatological disorders.

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2.3. Commensalism

As commensal residents of human skin, Malassezia species establish homeostasis through lipid-dependent colonization in sebaceous-rich niches, typically without inducing inflammation in immunocompetent hosts. Commensalism involves competitive pathogen exclusion, TLR2-mediated immune tolerance, and free fatty acid release to maintain barrier integrity. This symbiotic equilibrium, however, transitions to pathogenicity under dysbiotic conditions—including host immune compromise, cutaneous barrier disruption, or alterations in sebum composition—where commensal strains evolve into pathobionts via upregulated virulence expression (e.g., biofilm formation, inflammatory protease secretion). Symbiotic maintenance of Malassezia depends on PRRs-mediated immune recognition with bidirectional regulation of the CARD9/Th17-Treg axis. Barrier functional integrity and sebaceous microenvironmental homeostasis are central factors in preventing flora imbalance, which, when disrupted will trigger an inflammatory cascade response.

2.4. Opportunistic pathogenicity

The opportunistic pathogenicity of Malassezia fungi arises when compromised host defenses (e.g., impaired epidermal barrier, immunosuppression) or microenvironmental alterations (pH elevation, sebum composition changes) disrupt their commensal equilibrium. Under such dysbiotic conditions, these yeasts undergo pathogenic transformation through upregulated secretion of virulence factors (lipases, phospholipases, and aspartyl proteases), hyphal transition enhancing tissue invasion, biofilm formation conferring antimicrobial resistance, and activation of inflammatory cascades via TLR2/NF-κB and NLRP3 inflammasome pathways [3,4]. This culminates in dermatopathological manifestations ranging from pityriasis versicolor and seborrheic dermatitis to systemic infections in immunocompromised hosts.

3. Pathogenesis

As a lipophilic yeast, Malassezia typically resides as a commensal on human skin under normal conditions but can transform into an opportunistic pathogen under specific triggers, causing various dermatological conditions such as pityriasis versicolor, Malassezia folliculitis, seborrheic dermatitis with dandruff, atopic dermatitis, and psoriasis. There are two possible mechanisms that may cause follicular inflammation by Malassezia yeast. The first mechanism is caused by the lipase and phospholipase activity of Malassezia yeast. Malassezia secretes enzymes that hydrolyze host sebum, acquiring nutrients and triggering inflammatory cascades that drive various dermatoses (e.g., seborrheic dermatitis, pityriasis versicolor, and folliculitis). Specifically, Malassezia lipases decompose sebum triglycerides into free fatty acids (FFAs), which compromise skin barrier integrity and increase stratum corneum permeability, facilitating microbial invasion. FFAs are further metabolized via the cyclooxygenase (COX) pathway into prostaglandin E_2 (PGE_2), inducing erythema and pruritus. The second possible mechanism is caused by the ability of Malassezia yeast in vitro [1]. The core pathogenesis of Malassezia's in vitro virulence lies in a tiered cascade: environmental adaptation (lipid utilization) , virulence expression (enzyme/morphology), and immune evasion (biofilm formation). For in vitro cultivation, exogenous long-chain fatty acids (C12-C24) must be supplemented due to the absence of fatty acid synthase genes (*FAS1/FAS2*) in Malassezia, rendering it incapable of de novo fatty acid synthesis. Malassezia colonization density positively correlates with age and sebaceous gland activity, with higher prevalence observed in males, and individuals in hot/humid climates, potentially mediated by excessive sweating.

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3.1. Seborrheic dermatitis

Seborrheic dermatitis (SD) is a chronic, relapsing inflammatory skin disorder characterized by erythematous patches with greasy, yellowish scales preferentially affecting sebum-rich areas: the scalp, face (nasolabial folds, eyebrows, and ears), and upper trunk. It manifests across a spectrum from mild dandruff (pityriasis sicca) to severe inflammatory plaques. Malassezia's yeast-to-hypha transition (induced by pH>6.0 or sebum>150μg/cm²) enhances virulence through increased lipase secretion and biofilm formation, mirroring pathogenic mechanisms in Candida albicans. The pathogenesis of seborrheic dermatitis arises from a self-perpetuating triad of dysfunction: Malassezia lipase-mediated hydrolysis of sebum triglycerides releases pro-inflammatory free fatty acids (e.g., oleic acid) that disrupt stratum corneum integrity; genetic/epithelial barrier defects (e.g., filaggrin mutations) permit fungal antigen penetration, triggering TLR2/MyD88-dependent NF-κB activation and IL-17/IL-23 axis polarization; resultant epidermal hyperproliferation and aberrant differentiation amplify sebum production, further fueling Malassezia overgrowth and protease-mediated PAR-2 activation that induces pruritus and inflammation—ultimately establishing a feed-forward cycle of cutaneous dysbiosis [5,6].

3.2. Pityriasis versicolor

Pityriasis versicolor is a superficial fungal skin disease caused by the overproliferation of Malassezia spp., characterized by well-demarcated patches of abnormal pigmentation (either hyperpigmentation or hypopigmentation) on the skin surface, accompanied by fine, bran-like scales. The condition predominantly affects sebum-rich areas such as the chest, back, neck, and shoulders. Any skin condition that causes increased moisture, altered surface lipids, disruption of the stratum corneum barrier function, or aberrant immune responses can encourage commensal Malassezia overgrowth [7]. The metabolites of Malassezia fungi, particularly azelaic acid, potently inhibit tyrosinase activity and directly damage melanocytes, resulting in characteristic hypopigmented macules. Electron microscopy reveals reduced melanosome size and impaired melanin transfer in affected skin. Enzymes released by Malassezia (e.g., lipases) oxidize epidermal unsaturated fatty acids, generating dicarboxylic acids. Tyrosinase activity within melanocytes, the key enzyme in melanin synthesis, is inhibited by these compounds, which also directly impair melanocyte function [8,9]. Concurrently, certain strains may induce hyperpigmentation through pigment production or inflammatory responses, contributing to the classic "versicolor" (multicoloured) appearance.

3.3. Atopic Dermatitis (AD)

Atopic Dermatitis (AD) is a chronic inflammatory skin disorder characterized by core pathogenic mechanisms of skin barrier dysfunction and immune dysregulation. Its clinical manifestations include intense pruritus, recurrent eczematous lesions, and age-specific distribution patterns. A protein derived from Malassezia globosa—designated MGL_1304—has been identified in the sweat of patients with Atopic Dermatitis (AD). This protein may act as a potential allergen triggering AD-associated skin inflammation, and the allergic response to MGL_1304 exhibits a positive correlation with AD severity [4]. Epidermal barrier damage (e.g., in MC903-induced mouse AD models) can promote the overgrowth of Malassezia. The mechanisms involve atypical skin lipid metabolism (notably diminished ceramide levels) and reduced production of antimicrobial peptides, fostering a nutrient-abundant environment for the fungus. The diminished presence of beneficial bacterial flora, such as Staphylococcus epidermidis, reduces its competitive suppression of Malassezia.

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Simultaneously, Staphylococcus aureus (S. aureus) and Malassezia can establish a synergistic pathogenic association. Secreted enterotoxins from S. aureus (e.g., TSST-1) can augment the allergenic potential of Malassezia, whereas fungal metabolites supply essential nutrients for bacterial proliferation.

4. Treatment and future perspectives

4.1. Treatment

Antifungal Agents: Antifungal agents remain the cornerstone for treating Malassezia-associated diseases (e.g., seborrheic dermatitis, pityriasis versicolor), yet their efficacy and safety profiles vary significantly: Topical azoles(e.g., ketoconazole shampoo) offer 70.2% efficacy in mild cases with minimal side effects but high relapse rates. Systemic azoles(e.g., itraconazole) are effective for severe infections but require liver function monitoring due to hepatotoxicity. Combination therapies (e.g., azoles + thymol) achieve synergistic effects (87.5% synergy rate) and reduce drug resistance. Key limitations include drug resistance (via ERG11 mutations) and systemic toxicity of polyenes (e.g., amphotericin B nephrotoxicity).

Corticosteroids and Immunomodulators: Corticosteroids and immunomodulators are adjunctive therapies for Malassezia-associated dermatoses (e.g., seborrheic dermatitis, atopic flare), targeting inflammation rather than fungal eradication. Topical corticosteroids provide rapid symptom relief but carry risks of skin atrophy and rebound flares upon discontinuation. Calcineurin inhibitors (tacrolimus) offer sustained remission without atrophy, though with an initial burning sensation. Systemic agents like JAK inhibitors (tofacitinib) benefit refractory cases but increase herpes zoster risk. Critical safety measures include: gradual steroid tapering to prevent adrenal insufficiency, infection screening before immunomodulator use, and combination therapy with antifungals to reduce recurrence. Overall, immunomodulators outperform corticosteroids in maintenance therapy due to lower tachyphylaxis and better safety profiles.

Essential Oils: Essential oils demonstrate significant potential against Malassezia-associated dermatoses (e.g., seborrheic dermatitis, pityriasis versicolor) through dual antifungal and anti-inflammatory mechanisms. Key active components like cinnamaldehyde disrupt fungal membranes and biofilms with MICs while lemongrass oil reduces TNF-α by 40%. Synergistic combinations (e.g., thyme oil + chlorhexidine) enhance efficacy by 33.3% and reduce drug resistance. However, safety concerns include phototoxicity from citrus essential oils (bergamot/lemon) and dermal burns from undiluted phenolic oils (oregano/cinnamon).

4.2. Future perspectives

Antimicrobial peptides such as Satanin 1 exert an antimicrobial effect by disrupting fungal cell membranes (MIC 5–12.5 μg/mL), especially against drug-resistant strains (e.g., fluconazole-resistant Malassezia axonica), but in vivo pharmacokinetics (e.g., antiprotease degradation capacity) need to be optimized to improve. Antimicrobial fatty acids (e.g., hydroxy fatty acids) produced by Malassezia (e.g., M. sympodialis) kill Staphylococcus aureus but may induce bacterial resistance (e.g., Rel gene mutations). Future endeavors necessitate the formulation of "precision interference" tactics, including the manipulation of acidic environments to augment specific antimicrobial properties and the surveillance of drug evolution. Rose extract (rich in polyphenols) in combination with Coptis chinensis extract (mainly berberine) (ML extract) to make Malassezia furfur (M. furfur) by disrupting ergosterol synthesis and increasing cell membrane permeability. Leakage of cell

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contents. Scanning electron microscopy showed holes and folds on the cell surface, and in a mouse model of seborrheic dermatitis, ML extract reduced the pro-inflammatory factor IL-6/TNF-α by 68% and increased the skin barrier repair rate by 45% [10].

5. Conclusion

Malassezia yeasts appear to exemplify what might be characterized as the complex and dynamic nature of the host-microbe relationship. While seemingly constituting essential members of the healthy skin microbiome, apparently contributing to barrier integrity and microbial competition, their transition to pathogenicity under specific host and environmental conditions tends to suggest what appears to be significant dermatological diseases. What this review seems to indicate is that the shift from commensalism to pathogenicity is not inherently linked to the yeast itself but appears to represent a consequence of a multifaceted interplay between host factors (e.g., sebum composition, immune status, genetic susceptibility, barrier dysfunction), microbial factors (e.g., strain-specific virulence traits, metabolic reprogramming, morphogenic switch to hyphae, production of immunomodulatory metabolites and allergens like MGL_1304), and environmental triggers (e.g., humidity, temperature). What seems especially noteworthy in this analytical context are the key pathogenic mechanisms that appear to have been elucidated, including what tends to be characterized as disruption of the skin barrier through lipase/phospholipase activity, induction of inflammation via non-immunogenic irritation and specific immune responses, dysregulation of pigmentation (as seen in pityriasis versicolor), and what appears to be synergistic interactions with bacteria like Staphylococcus aureus. Given the complexity of these theoretical relationships, diseases such as seborrheic dermatitis, pityriasis versicolor, and atopic dermatitis seem to underscore what appears to be the substantial clinical impact of this dysbiosis. The research suggests that contemporary therapeutic techniques mostly depend on antifungal drugs, corticosteroids, and immunomodulators. Nevertheless, it seems that further interpretive analysis is necessary, as the future appears to shift from broad-spectrum antibiotic strategies towards what constitutes precision medicine.

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