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Review

Research Progress on the Exacerbation of Lipid Metabolism by *Malassezia* and Its Impact on the Skin Barrier Function

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Abstract: The study of the fungal communities of the skin constitutes a pivotal component of skin microbiome research. Within these communities, the genus *Malassezia* stands out as a major constituent, representing 50% to 80% of the total fungal colonization on the skin of healthy individuals. The excessive growth or metabolic irregularities of this genus are intimately connected with the onset of various skin disorders that are intrinsically linked to its lipid-dependent nature. Cutaneous lipid metabolism is indispensable for maintaining the skin barrier function and skin health. *Malassezia* possesses the ability to encode multiple lipase genes, and the secretion of these lipases plays a pivotal role in the survival strategies of the fungi. This review explores recent advances in the ecological niche of *Malassezia* in skin microecological homeostasis, its mechanism of disrupting skin lipids through catabolic metabolites, and the relationship between this disruption of the skin lipid barrier and skin diseases. This review offers a reference for future research on the mechanisms by which *Malassezia* affects lipid metabolism and provides a theoretical foundation for the development of innovative therapeutic approaches for dermatological conditions.

Keywords: *Malassezia*; skin lipid metabolism; free fatty acids; skin diseases; mechanistic pathways

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1. Introduction

Malassezia in Skin Microecology

As the first line of defense between the body and the external environment, the skin not only protects internal organs but also serves as a habitat for various microorganisms [1]. Numerous studies have confirmed that the skin microbiota plays a crucial role in maintaining skin homeostasis, specifically by preserving the integrity of the skin barrier function and promoting the regeneration of skin appendages [2,3]. Based on whole-metagenome shotgun sequencing, the skin microbiota is predominantly composed of Actinobacteria,

with a rich abundance of Gram-positive bacteria, such as Staphylococcus, Corynebacterium, and Bacillus, while *Malassezia* is more widely distributed among fungi [4–7].

Malassezia, a lipid-dependent basidiomycetous yeast, inhabits the skin and mucosa of humans and other warm-blooded animals [8], constituting a significant component of the skin microbiome (Figure 1). While presenting as skin commensals, *Malassezia* species are also associated with various skin diseases, including pityriasis versicolor (PV), *Malassezia* folliculitis (MF), seborrheic dermatitis/dandruff (SD), atopic dermatitis (AD), and psoriasis [9–11]. This genus currently includes 17 species, as shown in Table 1 [9,12–15]. Importantly, multiple *Malassezia* species or genotypes can cause unique or similar pathologies and exhibit varying antifungal susceptibilities [16].

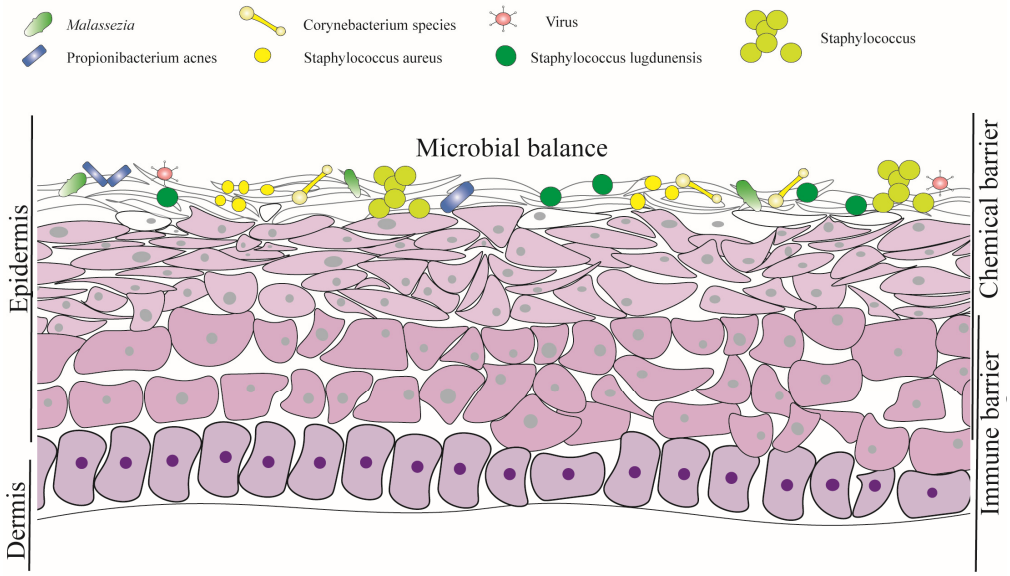


Figure 1. The barrier function of skin.

Table 1. *Malassezia* species on the skin surface.

***Malassezia* Species**	**Primary Distribution**	**Disease Associations**
Human-Associated		
M. furfur	Unclear. Human skin via culture, less so in molecular studies. Only species found in blood and urine	Neonatal-invasive/septic infections
M. arunalokei	Rare, human skin, India	
M. yamatoensis	Rare, human skin	
M. slooffiae	Rare, human skin, occasionally animals	
M. japonica	Rare, human skin, Japanese female	Unknown, reported in atopic dermatitis
M. obtusa	Rare, human groin, nasal vestibule, and also from animals	Unknown, reported in atopic dermatitis
M. obtusa	Rare, human groin, nasal vestibule, and also from animals	Unknown, reported in atopic dermatitis

Table 1. *Cont.*

Malassezia Species	Primary Distribution	Disease Associations
M. restricta	Skin of all humans, ear, face, scalp; domestic cats	Dandruff/seborrheic dermatitis, pityriasis versicolor
M. globosa	Skin of all humans, face, scalp, back	Dandruff/seborrheic dermatitis, pityriasis versicolor
M. sympodialis	Skin of all humans, face, scalp	Atopic eczema
M. dermatis	Rare, human skin	Mostly unknown, reported changes in atopic dermatitis
Animal Associated		
M. equina	Horse	Healthy and diseased skin
M. pachydermatis	All animals, likely very diverse and species-specific associations	Healthy and diseased skin of many animals, potential role in inhalational allergy
M. nana	Domestic cat, cow, horse ear	Healthy and diseased skin
M. caprae	Goat	
M. brasiliensis	Parrot (Brazil)	
M. cuniculi	Rabbit	
M. psitaci	Parrot (Brazil)	

Malassezia exhibits remarkable niche-specific adaptive evolution characteristics [17] that are highly adapted to lipid-rich and carbohydrate-poor cutaneous microenvironments [18]. This adaptability is coordinated with its lipophilic nature. This genus possesses the ability to encode multiple lipase genes, and the secretion of these lipases plays a significant role in the survival strategies of the host fungi and their pathogenic mechanisms [19].

The interaction between *Malassezia* and the host is complex: it is usually symbiotic but can also be pathogenic [20]. *Malassezia* invades the skin through multiple pathways, such as epidermal injury, hair follicles, sweat glands, sebaceous glands, immunosuppression, microbial community imbalance, environmental factors, and genetic factors. The molecular biological mechanisms involve multiple levels, including the fungal surface structure, secreted enzymes and toxins, immune escape mechanisms, and the host's immune response. *Malassezia* can be directly recognized by the host, either directly through membrane-bound pattern recognition receptors or indirectly through inflammatory metabolites released by the hydrolysis of sebum by fungal lipases and proteases [21–23]. Additionally, one mechanism through which *Malassezia* interacts with the immune system involves the production of specific allergens. Approximately half of adult patients with AD have allergen-specific immunoglobulin E (IgE) and T-cell responses to *Malassezia* [24].

The following are the primary molecular biological mechanisms of skin invasion by *Malassezia*:

(1) Surface Structure and Adhesion Factors

Cell Wall Components: The cell wall of *Malassezia* is rich in various components, including mannan, glucan, and phospholipids. These components are not only crucial for maintaining the structural integrity of the fungus but may also be involved in host cell adhesions.

Adhesins: Multiple adhesins, such as mannan-binding proteins, are expressed on the surface of *Malassezia*. These adhesins can bind to receptors on the surfaces of host

cells, aiding in the attachment of the fungus to the skin and providing a foundation for further invasion;

(2) Enzyme Secretion

Lipase: *Malassezia* can secrete lipase, an enzyme that breaks down triglycerides and fatty acids in sebum, generating free fatty acids. These free fatty acids not only provide a carbon source for fungal growth but may also damage the host's skin barrier.

Proteases: *Malassezia* secretes proteases, which degrade proteins in the host's extracellular matrix, such as collagen and elastin, helping the fungus to penetrate deeper into the skin.

Chitinase: chitinase is capable of degrading chitin in the host's extracellular matrix, facilitating fungal invasion and spread;

(3) Toxins and Metabolites

Organic Acids: The metabolic activities of *Malassezia* produce certain organic acids, such as acetic acid and propionic acid. These acidic metabolic products can lower the pH value of the skin surface, inhibiting the growth of other microorganisms. Simultaneously, they may also cause inflammatory reactions on the skin.

Fatty Acids: some fatty acids produced by *Malassezia*, such as oleic acid, may have toxic effects capable of affecting the function and immune response of host cells;

(4) Immune Evasion Mechanisms

Mannans: the *Malassezia* cell wall contains mannans, which interfere with the recognition of host immune cells, enabling the fungus to evade the host's immune clearance.

Phospholipase: the phospholipase secreted by *Malassezia* can degrade the phospholipid components of the host cell membrane, interfering with the function and signal transduction of host cells, thereby evading the host's immune response;

(5) Host Immune Response

Immunological Tolerance: In healthy individuals, the host's immune system typically exhibits a degree of tolerance to *Malassezia*; thus, a strong immune response is not triggered. However, when the fungal load is excessive or the host's immune system is compromised, inflammatory reactions may be triggered.

Inflammatory Cytokines: *Malassezia* infection may activate the host's inflammatory response, releasing various inflammatory cytokines (such as IL-1β and TNF-α), leading to skin redness, swelling, itching, and inflammation.

Antifungal Immunity: The host's immune cells (such as macrophages and dendritic cells) can recognize and phagocytose *Malassezia* and kill the fungi by releasing antimicrobial peptides and reactive oxygen species. However, *Malassezia* can also evade the host's immune clearance through the aforementioned immune evasion mechanisms;

(6) Host Genetic Factors

Genetic Susceptibility: Some individuals may exhibit a higher susceptibility to *Malassezia* infection due to genetic factors. This may be related to the host's skin barrier function, immune response strength, or expression levels of inflammatory factors;

(7) *Malassezia* Extracellular Vesicles (MalaExs)

Extracellular vesicles represent a current research hotspot. *Malassezia* communicates with its host through the release of MalaExs, which carry allergens and induce inflammatory cytokine responses [25]. For instance, MalaExs contain miRNAs as cargo and can deliver functional mRNAs and miRNAs to recipient host cells, thereby interfering with the host's ribonucleic acid mechanisms, silencing host immune genes, and leading to infection [26].

In summary, the molecular and biological mechanisms of *Malassezia* skin invasion constitute a complex process involving various aspects, such as the fungal surface structure, enzyme secretion, toxin production, immune evasion mechanisms, and the host's immune response.

In healthy skin, *Malassezia* utilizes essential nutrients for growth without causing disease. However, when this process is disrupted, *Malassezia* yeast alters the skin's lipid composition through the aforementioned pathways under different circumstances, leading to skin conditions such as dandruff and pityriasis versicolor, as well as more severe inflammatory diseases like seborrheic dermatitis and atopic dermatitis (AD) [27].

Understanding these molecular biological mechanisms will facilitate the development of targeted prevention and treatment strategies to address skin infections and inflammation caused by *Malassezia*.

2. Lipid Metabolism of Skin

2.1. Structure and Function of Sebaceous Glands

Sebaceous glands are holocrine glands found throughout the body, except for the palms, soles, and dorsum of the feet, with a higher concentration on the face and scalp [28,29]. Located in the dermis, their primary function is to produce and secrete sebum [30]. In human fetuses, sebaceous glands develop from the shallowest protrusions on the developing hair follicles between the 13th and 16th weeks. Once fully formed, the glands remain attached to the hair follicles via ducts, through which sebum flows into the follicular canal and reaches the skin surface [28,31,32]. The secreted sebum serves as a delivery system for antibacterial lipids and antioxidants, facilitating substance transport within and on the skin, and exhibiting natural photoprotective activity. It possesses inherent antibacterial properties, promotes skin health, and exhibits anti-inflammatory functions, while also regulating the activity of xenobiotics [33].

The sebaceous membrane in the sebaceous glands, the stratum corneum, and its intercellular structural substances collectively form a solid physical barrier for the skin, and they work synergistically to protect against external aggressions and enhance the moisturizing capacity of the stratum corneum. Simultaneously, they maintain the acid–base balance of the skin's surface, effectively mitigating potential damage to the stratum corneum [34,35]. The function of sebaceous glands is regulated by various compounds, including androgens, estrogens, retinoids, liver-X receptor (LXR) series, growth hormones, and hydrocortisone [36]. The indicator for determining sebaceous gland activity is sebum secretion, with squalene and wax esters serving as the most reliable markers for measuring sebum production [37], as they are unique to sebum and not influenced by lipids from other skin cells [38,39].

2.2. Mechanism of Sebum Production and Secretion

Skin lipids primarily consist of sebaceous gland lipids and intercellular lipids, with sebaceous gland lipids accounting for 75% to 90% and mainly distributed on the skin surface. They are primarily composed of triglycerides (60%), wax esters (25%), squalene (12%), cholesterol esters (2%), and a small amount (less than 1%) of cholesterol. These lipids have strong fluidity [31,40]. Sebaceous gland lipids play a crucial role in maintaining and enhancing human skin beauty, as well as in skin repair. They not only lubricate the skin but also inhibit the growth of certain pathogenic microorganisms [41]. Intercellular lipids originate from the lamellar bodies of spinous layer cells and account for 10% to 25% of the total. They mainly consist of ceramides, cholesterol, free fatty acids, triglycerides, and other components and have relatively low fluidity [22].

The sebaceous glands produce and secrete sebum through the "holocrine secretion" mechanism [42]. Specifically, precursor cells within the basement membrane undergo continuous division to replenish the gland. During migration, these cells progressively synthesize lipids and accumulate them into droplets. Ultimately, the cells swell and rupture, releasing lipids into the glandular duct. Throughout this process, the nucleus and subcellular structures gradually degenerate. The ruptured cells, along with their lipid contents, are transported via the glandular duct to the skin surface as sebum. When the cells approach the duct of the sebaceous gland, they disintegrate and release their contents through holocrine secretion. Only neutral lipids reach the skin's surface, whereas proteins are digested and recycled during the cellular breakdown process [43]. The differentiated cell population is maintained through mitotic activity in the peripheral cells of the sebaceous gland lobule and in the aggregates of undifferentiated cells extending into the lobule body. Once formed, under the continuous influence of circulating hormones, each sebaceous gland lobule continuously produces differentiated cells that gradually accumulate sebum as they move toward the sebaceous gland duct and ultimately release their contents into the duct. The sebum is then excreted through the glandular duct and combines with the stratum corneum in the hair follicle, eventually being discharged to the skin surface through the follicular pore [44,45].

2.3. Sebaceous Gland Lipid Secretion Pathway

The lipids secreted by the sebaceous glands initially do not contain fatty acids; fatty acids are formed by the hydrolysis of triglycerides by commensal bacteria within the hair follicles.

(1) Lipid Secretion Pathway of Keratinocytes: Keratinocytes synthesize lipid precursors and secrete them in the form of lamellar bodies. These lipid precursors are catalyzed by lipid-synthesizing enzymes to produce lipids. As keratinocytes grow, metabolize, and decompose, the lipids dispersed among them are distributed to the skin surface;
(2) Lipid Metabolism Pathway of Skin Microbiota: A large number of microbial flora survive on the skin surface, with most microorganisms feeding on keratinocyte debris or lipids. During metabolism, they can produce lipids, such as short-chain fatty acids;
(3) Enzymes Related to Lipid Metabolism: Enzymes involved in lipid metabolism, such as kallikrein, enzymes for the elongation of very-long-chain fatty acids, hydrolytic enzymes, and lipid-synthesizing enzymes, participate in the skin barrier function and structure.

These pathways and mechanisms work together to maintain the balance of skin lipids, affecting the skin barrier function and skin health. Understanding these pathways is helpful for developing therapeutic strategies for skin lipid metabolism-related diseases.

3. Lipid Metabolism of Skin Diseases

3.1. Skin Lipid Barrier

The skin barrier is an extraordinary interface with a unique lipid organization, and its barrier function is primarily embodied in the stratum corneum, the outermost layer of the skin. The stratum corneum consists of dead cells, with highly organized lipid lamellae in the intercellular spaces, exhibiting a crystalline arrangement of saturated straight lipid chains. As the lipid matrix forms a unique continuous pathway, lipids play a crucial role in the permeation of compounds through the stratum corneum. The main lipid categories are ceramides (CERs), cholesterol (CHOL), and free fatty acids (FFAs). The intra-lamellar connections provided by 30-carbon ω-hydroxy acid lipids may represent a key factor in assembling the intercellular lamellae and lamellar granules of granular cells.

The analysis of the lipid matrix is vital for understanding the skin barrier function, not only in healthy skin but also in inflammatory skin diseases where the skin barrier is impaired. Understanding the composition and spatial structure of the skin's lipid barrier, as well as regulating the lipid composition, holds promise for improving the skin barrier in inflammatory skin diseases, thereby achieving therapeutic, reparative, and maintenance goals for the skin.

3.2. Lipid Metabolism Abnormalities and Skin Diseases

Excessive or low sebum production, abnormal sebum composition, or uneven lipolysis are manifested as abnormalities in skin lipid metabolism, and these changes can disrupt the normal structure and function of the skin and lead to skin problems.

When the skin produces too much sebum, elevated levels of androgens stimulate the sebaceous glands and increase sebum production, making pores prone to clogging and causing acne [33,46]. In patients with acne, the sebum contains a higher proportion of components such as free fatty acids and squalene, which are prone to oxidation and subsequently trigger inflammatory responses. In the context of excessive sebum secretion coupled with an imbalance in microbial flora, seborrheic dermatitis occurs, making the skin surface oily and further exacerbating inflammation [47].

A decrease in sebum secretion can also lead to impaired skin barrier functioning. In psoriasis, reduced sebum secretion is observed, and the peroxidation of squalene in the skin's lipids is exacerbated. This can trigger or exacerbate symptoms. The occurrence of atopic dermatitis (eczema) is closely related to decreased sebum secretion. Here, the levels of ceramides and free fatty acids in the sebum are reduced, and there is also a lack of anti-inflammatory lipids (such as arachidonic acid metabolites). This results in a weakened lipid layer on the skin's surface, increases water loss from the skin, and subsequently impairs the skin barrier function, triggering atopic dermatitis (eczema) [48].

Moreover, abnormal sebum components can weaken the skin barrier function, making the body more susceptible to external stimuli and triggering immune responses. When the composition of the sebum is abnormal, particularly with an increase in components such as oleic acid and squalene, *Malassezia* metabolizes these lipids, producing metabolites that interfere with skin pigment cells, leading to pigmentation or depigmentation and triggering pityriasis versicolor. When the amounts of structural lipids, such as ceramides, in the stratum corneum decrease, it causes abnormalities in the skin barrier function, resulting in dry and flaky skin, and subsequently inducing ichthyosis [49].

3.3. Molecular Mechanisms and Pathways of Skin Lipid Regulation

The molecular mechanisms and pathways of skin lipid regulation are complex biological processes involving various signaling molecules and metabolic pathways. The following are some key mechanisms and pathways:

The IL1 and WNT Signaling Pathways:

Ling-juan Zhang et al. revealed the molecular mechanisms underlying the dynamic changes in fat during skin development and wound healing. They found that the processes of adipogenesis and lipolysis–re-adipogenesis are dynamically regulated by the IL1–pCREB and WNT–β-catenin pathways [50,51]. IL1 signaling promotes the differentiation of skin adipocytes by activating the NFκB–CREB pathway and inhibiting WNT–β-catenin pathway activity;

The Zinc Finger Protein 750 (ZFP750) Regulatory Pathway:

Studies have shown that the absence of ZFP750 alters the composition of epidermal lipids, leading to impaired skin permeability barrier functioning. The deletion of the ZFP750 gene results in changes in the expression of 1722 genes, including those involved

in keratinization, cell migration, proliferation, and lipid metabolism. Butera et al. revealed that ZFP750, as a key transcription factor in skin development, directly and/or indirectly regulates the expression of key enzymes involved in ceramide biosynthesis [52], which is crucial for skin barrier permeability. This finding will contribute to understanding the pathogeneses of several human skin diseases;

The Peroxisome Proliferator-Activated Receptor (PPAR) Pathway:

PPARs play a crucial role in skin physiology, particularly in lipid metabolism and inflammatory responses [53,54]. PPARα, PPARβ/δ, and PPARγ have distinct roles in regulating skin lipid metabolism. For example, PPARα is involved in the regulation of lipid metabolism in the skin, while PPARγ plays a key role in modulating sebaceous gland lipid secretion. CD36 is an important downstream marker of the FAO-PPARγ pathway and is currently the only known fatty acid transporter that can bind to components in the extracellular matrix;

The Autophagy Pathway:

Autophagy also plays a significant role in the regulation of lipid metabolism, especially in the degradation of lipid droplets and the reuse of lipids.

These molecular mechanisms and pathways work together to finely regulate the synthesis, secretion, and metabolism of skin lipids, maintaining the skin barrier integrity and function. Understanding these pathways is instrumental in developing therapeutic strategies for skin lipid-related diseases.

4. Malassezia and Sebum Metabolism

4.1. Effect of Malassezia on Sebum Composition

Malassezia, as a lipophilic and lipid-dependent yeast, has had its lipid dependency confirmed through the genomic sequences of 14 species within this genus [55,56]. Unlike other fungi, *Malassezia* lacks the ability to synthesize certain fatty acids due to the absence of fatty acid synthase (FAS) genes in its genome. It needs to obtain these fatty acids from the host's sebum. Its metabolism relies on esterases and lipases [57]. Genomic analyses of multiple *Malassezia* species have shown that the number of lipase-encoding genes is significantly higher in these organisms than in other fungi. They can secrete a variety of lipases with broad-spectrum activity that hydrolyze triglycerides in sebum into free fatty acids and glycerol. The free fatty acids are further broken down into its main energy source [19,56]. However, *Malassezia* has unique nutritional requirements. Despite the versatility of its lipases, it can only metabolize saturated fatty acids due to the lack of Δ9 desaturase. As a result, saturated fatty acids are consumed, while unsaturated fatty acids remain in the skin [58,59]. In addition, the cell membrane structure of *Malassezia* requires specific lipids to maintain its structure and function, such as diacylglycerols and sphingomyelins. Moreover, *Malassezia* not only faces nutritional limitations in the skin environment but also needs to adapt to the relatively low oxygen levels on the skin surface. Lipid metabolism under hypoxic conditions can produce ATP and other necessary metabolic intermediates, such as NADH, FADH2, acetyl-CoA, ketone bodies, succinate, fumarate, and hydrogen peroxide, allowing *Malassezia* to survive in the hypoxic environments of the skin surface and follicular orifices [60]. *Malassezia* obtains energy by decomposing lipids in the host's sebum and synthesizes cellular membrane components. At the same time, it can adapt to hypoxic environments, successfully establishing and securing its unique ecological niche on the skin surface. *Malassezia* degrades sebum, releasing various fatty acids from triglycerides, and consumes the specific saturated fatty acids necessary for its proliferation. Experiments have shown that changes in the sebum composition over time are a direct result of *Malassezia* metabolism [61]. *Malassezia* produces free fatty acids by decomposing lipids in sebum, thereby affecting the composition of sebum and the skin's acid–base balance. It also triggers

inflammation and oxidative stress, altering the skin's microecological environment and increasing the risk of skin problems [62].

4.2. Interaction Between Malassezia and Sebaceous Glands

The interaction between *Malassezia* and sebaceous glands encompasses multiple aspects, such as metabolites, inflammatory responses, and signaling pathways, which collectively maintain this complex mechanism [57]. This interaction plays a role in maintaining the balance of skin flora and normal sebum secretion; however, in some cases, it can lead to the onset of skin diseases (Figure 2).

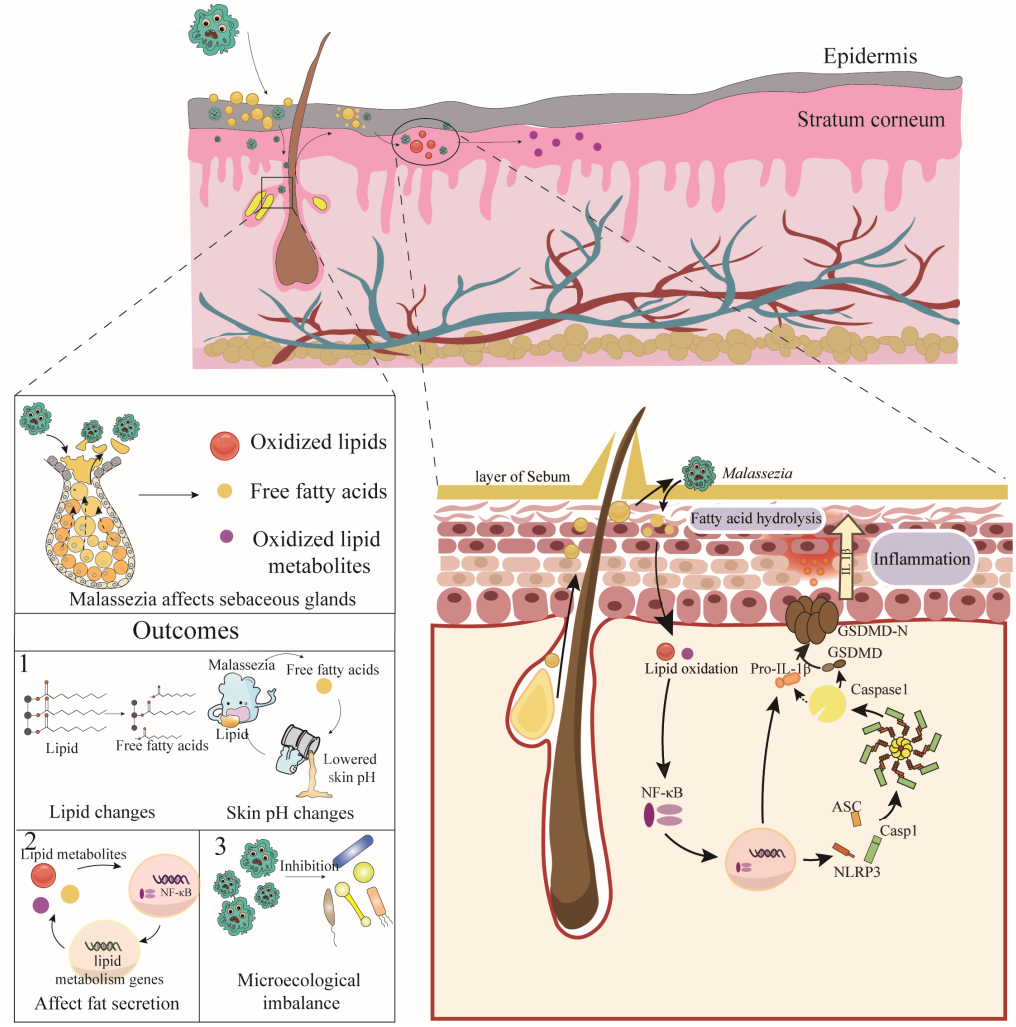


Figure 2. Interaction between *Malassezia* and sebaceous glands.

(1) The Lipase-Mediated Sebum Decomposition Process: The lipase released by *Malassezia* can effectively decompose triglycerides produced by sebaceous glands, generating free fatty acids, such as oleic acid. These free fatty acids directly act on the sebaceous glands, stimulating them to secrete more sebum, forming a positive feedback loop. The additional sebum produced by the sebaceous glands provides more nutrients for *Malassezia*, promoting its growth and metabolism, and further exacerbating sebum secretion and decomposition [63,64];

(2) Affecting Sebaceous Glands through Signaling Pathways: *Malassezia* metabolites activate specific signaling pathways (such as the NF-κB pathway) in sebaceous gland cells, thereby regulating the sebaceous gland function. This signaling effect leads to the release of more lipids by the sebaceous gland cells, enhancing the nutritional

supply to *Malassezia*. Additionally, the metabolites may also affect transcription factors within sebaceous gland cells, altering the expression levels of genes involved in lipid metabolism and making the sebaceous glands more sensitive and active under external stress [65,66];

(3) Altering the Sebaceous Gland Microenvironment to Promote *Malassezia* Proliferation: The metabolites of *Malassezia* alter the microenvironment of the sebaceous glands, making it more conducive to the growth of *Malassezia* [67]. For example, the free fatty acids generated by the decomposition of sebum by *Malassezia* acidify the skin's surface, creating a low-pH environment that is more favorable for *Malassezia* proliferation. At the same time, the fatty acids contained in sebum, such as oleic acid, provide abundant nutrients for *Malassezia*, promoting its rapid proliferation in the sebaceous gland area [68];

(4) Generating Oxidative Stress: The oxidative substances produced by *Malassezia* metabolism promote oxidative stress responses, exacerbating the metabolic activity of sebaceous glands. These substances induce oxidative stress in sebaceous gland cells, further activating local inflammatory responses in the skin and affecting the normal metabolic function of sebaceous glands. This oxidative stress response may further stimulate sebum production, causing the sebaceous glands to remain in an active state. Over time, the metabolic burden on the sebaceous glands will gradually increase, potentially leading to oily skin and subsequently causing issues such as clogged pores and acne [69];

(5) Regulating the Microbial Balance Around Sebaceous Glands: When sebaceous glands are actively secreting, *Malassezia* proliferation accelerates. This rapid growth may inhibit the development of other skin microorganisms, leading to an imbalance in the skin's microbiome [70]. For example, overly proliferating *Malassezia* can outcompete other commensal bacteria, potentially disrupting the skin's immune system responses [71,72]. Conversely, abnormalities in the sebaceous gland function may also cause an imbalance in the proliferation of *Malassezia* and other microorganisms, leading to inflammatory or infectious skin diseases [73].

4.3. Malassezia and Skin Lipid Barrier Disruption

Malassezia species secrete lipases and phospholipases to hydrolyze triglycerides and phospholipids in sebum, generating abundant free fatty acids (such as oleic acid), which directly disrupt cutaneous lipid homeostasis [74]. These free fatty acids not only enhance sebum production but also exacerbate barrier dysfunction through the mechanisms presented in Table 2.

Table 2. Key mechanisms of skin barrier disruption by *Malassezia* metabolites [75].

Target	Mechanism	Clinical Correlation
pH dysregulation	Inhibits antimicrobial peptide activity and barrier defense	Microbial colonization
Stratum corneum	Parakeratosis and reduced tight junction proteins	Transepidermal water loss
Lipid matrix	Ceramide/cholesterol ratio imbalance	Xerosis, desquamation
Immune barrier	Induces IL-1α/TNF-α release	Erythema and pruritus

Free fatty acids derived from *Malassezia*-mediated sebum decomposition stimulate sebaceous glands to hypersecrete sebum, establishing a "sebum overload–fungal proliferation" feedback loop. In seborrheic dermatitis, *Malassezia* species (such as *M. globosa* and

M. restricta) metabolize sebum into pro-inflammatory agents such as indole derivatives, further compromising the barrier integrity and inducing Th2-type immune dysregulation (such as aberrant IL-4 and IL-10 levels), thereby aggravating symptoms [74].

Malassezia cell wall components (such as mannans) and antigens evade immune recognition or hyperactivate immune responses, contributing to chronic inflammation and barrier impairment.

Host genetic factors (such as ZFP750 deficiency) or endocrine imbalances may heighten sensitivity to *Malassezia* metabolites, accelerating disease progression.

In summary, *Malassezia* drives a self-perpetuating cycle of "lipid dysregulation–barrier disruption–inflammatory amplification" via lipolytic activity, inflammatory induction, and immune crosstalk, ultimately leading to seborrheic dermatitis and related disorders. Targeting this cycle requires combinatorial strategies integrating antifungal agents, lipid metabolism modulators, and immunomodulatory interventions.

5. Prospects for the Application of Skin Lipid Metabolism Regulation in the Treatment of Malassezia-Related Skin Diseases

The skin combats *Malassezia* by maintaining the lipid barrier integrity (such as balancing the ceramide, cholesterol, and free fatty acid ratios) and regulating sebum secretion to limit nutrient acquisition (such as saturated fatty acids) [59,75]. Simultaneously, it inhibits *Malassezia*-secreted lipases from breaking down sebum into pro-inflammatory free fatty acids (such as oleic acid) and enhances lipid metabolic homeostasis through pathways such as ZFP750 and PPARs. This reduces oxidative stress and inflammatory cytokine release (such as IL-1α/TNF-α), thereby blocking the pathogenic cycle [50].

5.1. Treatment for Regulating Abnormal Skin Lipid Metabolism

Current approaches focus on disrupting pathogenic cycles by targeting lipid synthesis, breakdown, and transport processes to restore skin health. For diseases related to skin lipid metabolism, such as seborrheic dermatitis, acne, and rosacea, treatment strategies typically encompass various aspects, including topical treatment [76], systemic treatment, and lifestyle interventions. Some of the primary strategies are as follows:

(1) Topical Medications

Topical medications achieve maximized therapeutic efficacy through the precise targeting of pathological pathways, albeit with inherent limitations (Table 3).

Table 3. Topical medications that promote skin lipid metabolism [77,78].

Category	Mechanism	Limitations
Retinoids	Modulate keratinocyte differentiation, reduce sebum production	Skin irritation, dryness, erythema
Antifungals	Ergosterol synthesis disruption	Skin irritation, hepatotoxicity
Anti-androgens	Block androgen receptors, reduce sebaceous gland activity	Menstrual irregularities, hyperkalemia
Vitamin D analogs	Regulate keratinocyte proliferation and immune modulation	Local irritation, hypercalcemia
Salicylic acid	Exfoliates stratum corneum, unclogs pores	Dryness, irritation

(2) Laser and Radiofrequency Treatments

Sebaceous Gland Laser: Lasers can be used to destroy the sebaceous glands, thereby reducing sebum secretion. Side effects include redness, pain, and pigmentation.

Radiofrequency Microneedling: Radiofrequency energy is delivered to the sebaceous glands through microneedles to reduce sebum secretion. Side effects include redness, pain, and risk of infection;

(3) Plant-Based Active Ingredients

Plant-based active ingredients specifically denote the bioactive constituents derived from botanical extracts. Numerous plant-based active ingredients can affect the function of sebaceous glands through various mechanisms, reducing sebum secretion and thereby improving skin diseases related to abnormal lipid metabolism. Common plant ingredients and their mechanisms of action are described below.

Essential Oils: these oils, including tea tree oil, lavender oil, and hemp seed oil, possess antibacterial properties.

Anti-inflammatory Agents: these agents include *Polygala japonica* Houtt. [79,80], witch hazel, aloe vera, licorice extract, rosemary extract, chamomile extract, white willow bark extract, milk thistle extract, notoginseng extract, *Centella asiatica* extract, grape seed extract, olive extract, and green tea extract, among others.

Plant-based active ingredients exhibit multiple effects in regulating skin lipid metabolism, including anti-inflammatory, antioxidant, antibacterial, moisturizing, and wound-healing promotion effects. These ingredients can be used alone or in combination to improve the skin environment, reduce sebum secretion, and effectively treat and prevent skin diseases associated with abnormal lipid metabolism;

(4) Biological Therapy

Biological therapy is an emerging treatment approach that controls diseases through targeted drugs aimed at specific inflammatory mediators or immune cells (Table 4).

Table 4. Biological therapy of skin lipid metabolism [81,82].

Category	Mechanism	Limitations
Dupilumab	Blocks IL-4/IL-13 signaling	Local reaction, long-term safety unclear
Emerging Biologics	Target IL-13 or TSLP	Limited clinical date

5.2. Future Prospects

Advances in biotechnology are driving the development of novel biologics targeting pathways such as IL-4/IL-13 and WNT-β-catenin, which hold promise for improving the treatment efficacy and quality of life in *Malassezia*-associated inflammatory conditions like atopic dermatitis [83]. Combination therapies integrating these biologics with lipid metabolism modulators (such as PPARγ agonists), antifungal agents, or plant-derived components (such as green tea extract) aim to disrupt the "lipid dysregulation-barrier disruption-inflammation" cycle while minimizing the risks of monotherapy [54,63,64].

The next milestone involves optimizing synergistic regimens, such as pairing bio-logics with phototherapy or traditional immunosuppressants, to directly suppress *Malassezia* proliferation and inflammatory cascades through host lipid regulation. In addition, using engineered bacteria (such as *Staphylococcus hominis*) or bacterial preparations to regulate the flora of abnormal skin [84] will also represent a very important research direction in the future. Although biologics offer breakthroughs for refractory cases, further clinical

validation and strategy refinement are critical to balance their efficacy, safety, and long-term outcomes [85].

6. Conclusions

With the in-depth research on the relationship between *Malassezia* and skin lipid metabolism, regulating skin lipid metabolism has emerged as a potential strategy for the treatment of *Malassezia*-related skin diseases. By modulating the production and secretion of sebum, the nutritional source of *Malassezia* can be reduced, thereby inhibiting its overgrowth. Furthermore, regulating specific lipid components may help restore the skin's lipid barrier function and reduce inflammatory responses. Future research may focus on the development of new drugs and therapeutic approaches that directly target the regulation of skin lipid metabolism, aiming for more effective treatment outcomes. Strategies targeting the regulation of skin lipid metabolism are expected to provide new therapeutic directions for *Malassezia*-related skin diseases such as seborrheic dermatitis in clinical practice.

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Abbreviations

The following abbreviations are used in this manuscript:

PV	Pityriasis versicolor
MF	*Malassezia* folliculitis
SD	Seborrheic dermatitis/dandruff
AD	Atopic dermatitis
IgE	Immunoglobulin E
MalaExs	*Malassezia* extracellular vesicles
LXRs	Liver-X receptors
CERs	Ceramides

CHOL	Cholesterol
FFAs	Free fatty acids
PPARs	Peroxisome proliferator-activated receptors
FAS	Fatty acid synthase
ZFP750	Zinc finger protein 750

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