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REVIEW

Microbiome: Role in Inflammatory Skin Diseases

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Abstract: As the body's largest organ, the skin harbors a highly diverse microbiota, playing a crucial role in resisting foreign pathogens, nurturing the immune system, and metabolizing natural products. The dysregulation of human skin microbiota is implicated in immune dysregulation and inflammatory responses. This review delineates the microbial alterations and immune dysregulation features in common Inflammatory Skin Diseases (ISDs) such as psoriasis, rosacea, atopic dermatitis(AD), seborrheic dermatitis(SD), diaper dermatitis(DD), and *Malassezia folliculitis*(MF).The skin microbiota, a complex and evolving community, undergoes changes in composition and function that can compromise the skin microbial barrier. These alterations induce water loss and abnormal lipid metabolism, contributing to the onset of ISDs. Additionally, microorganisms release toxins, like *Staphylococcus aureus* secreted α toxins and proteases, which may dissolve the stratum corneum, impairing skin barrier function and allowing entry into the bloodstream. Microbes entering the bloodstream activate molecular signals, leading to immune disorders and subsequent skin inflammatory responses. For instance, *Malassezia* stimulates dendritic cells(DCs) to release IL-12 and IL-23, differentiating into a Th17 cell population and producing proinflammatory mediators such as IL-17, IL-22, TNF-α, and IFN-α.This review offers new insights into the role of the human skin microbiota in ISDs, paving the way for future skin microbiome-specific targeted therapies.

Keywords: skin microbiota, inflammatory skin diseases, atopic dermatitis, seborrheic dermatitis, rosacea, acne, psoriasis, diaper dermatitis, *Malassezia* folliculitis

Introduction

ISDs result from disturbances in the host defense system of the skin, often involving abnormal keratinocyte differentiation, sebaceous gland composition changes, propagation of pathogenic microorganisms, and immune-mediated inflammation. Common ISDs such as AD, psoriasis, rosacea, acne, DD, and MF are characterized by recurring cutaneous lesions and intense itching.The pathogenesis of ISDs is multifaceted, incorporating environmental and genetic factors, biological barriers to the skin microbial community, and immune system deficiencies.[1]

Various pathways in the inflammatory response contribute to the pathogenic process, primarily involving abnormal protein folding, cellular stress, disorder in the nuclear factor (NF)-κB, interferon activation, and other mechanisms.[2] The role of skin microbial barrier dysfunction and T cell-mediated immune response is crucial in the pathogenesis of AD. Similarly, psoriasis and rosacea exhibit various skin cell changes, including T lymphocyte infiltration and vascular proliferation.[3]

The human skin microbial community is diverse and influenced by factors such as age, body site, and gender. Different skin regions typically select distinct microbiota to adapt to the specific microenvironments, including temperature, sebum production, and sweat levels, at their occupied niche on the body site.[4] These commensals play a regulatory role in maintaining host health and disease by preventing invasion from pathogenic microorganisms, fostering host

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immune responses, and mounting appropriate defenses against potential breaches of the skin barrier by pathogenic microorganisms. For instance, *S. epidermidis* produces antimicrobial substances against pathogens, while *Propionibacterium acnes(P. acnes)* utilizes skin lipids to generate short-chain fatty acids, exerting anti-inflammatory effects and preserving host homeostasis.[5] In addition to the physiological factors that influence microbial colonization, the host also influences the composition of the flora through the immune system. For example, the host contributes to establishing and shaping the microbial community through keratinocytes (KC) of the epidermis, antimicrobial peptides (AMPs) from the sebaceous glands, lipid antimicrobials, and cytokines.[6]

Recent advancements in multi-omics sequencing technology and meta-gene analysis have revealed extensive interactions between the skin commensal flora and the skin immune system. The physiological properties of the skin and the immune system jointly regulate the composition and distribution of the skin flora. Simultaneously, microorganisms act on host cells through their bacteriophage composition and metabolites, influencing local and systemic immunity. The maintenance of cutaneous immune homeostasis relies on a delicate balance between the skin immune system and the flora. Thus, understanding the characteristics of the skin microbiome is imperative for comprehending the development and treatment of ISDs. Based on this, this article aims to systematically review microbial alterations and immune dysregulation in some common ISDs, including psoriasis, rosacea, AD, SD, DD, and *Malassezia folliculitis*. Additionally, it will explore the relationship between the composition/function of the human microbiome and the underlying mechanisms of skin diseases, providing new insights for clinical diagnosis and treatment.

The Characteristics of the Skin Microbiome

The skin, the largest organ of the human body, is colonized by a diverse array of microbiota, including bacteria, fungi, and viruses, which contribute to the protection against foreign pathogens. The skin microbiota encompasses both transient and resident microbial communities, with its composition influenced by various skin microenvironments, such as temperature, age, sebum, and sweat. Consequently, the skin microbiota exhibits a considerable level of diversity.[7] Notably, 90% of individuals harbor a "core" symbiotic microbial community. Within healthy skin, the predominant microbes belong to four primary phyla: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%). Furthermore, Corynebacterium (22.8%), Cutibacterium (23.0%), and *Staphylococcus* (16.8%) stand out as the dominant genera.[8]

Moreover, the skin comprises multiple niches, each characterized by distinct physiological properties and, consequently, harboring different microbiota adapted to these specific environments.[9,10] For instance, regions abundant in sebum are primarily populated by Cutibacterium and *Malassezia fungi*. Moist skin areas, such as armpits, predominantly host *Corynebacterium* and *Staphylococcus* bacteria. Dry skin regions, like the limb flexion side, are dominated by mixed populations of *Proteus, Xanthobacter*, and *Malassezia*.[9,11]

Skin microorganisms regulate the host response through interactions with KC, AMP, lipid antimicrobial agents, and cytokines, thereby enhancing skin homeostasis and barrier function. Such skin bacteria, coexisting symbiotically with the host, are known as symbiotic bacteria. These symbiotic bacteria are vital for the host's well-being, as they aid in preventing the invasion of pathogenic microorganisms and fostering host immune responses.[12] *Staphylococcus epidermidis* produces antibacterial substances against pathogens, while Cutibacterium acnes induces anti-inflammatory effects through the secretion of short-chain fatty acids((SCFAs)).[13] Epidermal bacteria and Corynebacterium help inhibit the colonization of *Staphylococcus aureus(S. aureus)* and maintain host homeostasis by forming porphyrins.

The Dysfunction of Skin Microbial Barrier

The epidermis, dermis, and deeper subcutaneous tissues collectively form a physical and chemical barrier against pathogens.[14] Additionally, an immune barrier includes a transient innate immune response and a robust adaptive immune response, also known as adaptive immunity. While in symbiosis with the host, the human skin microbiota acts to preserve the skin barrier function and is referred to as a commensal. However, in certain pathological conditions, significant alterations in the diversity, quantity, composition, and metabolism of skin microbiota can disrupt homeostasis and alter the ecological interaction between microorganisms and the host, triggering the release of surface AMP, recruitment of neutrophils, and production of interleukins to modulate the complement system and exacerbate skin inflammation.[5]

The onset of various skin diseases has been linked to disruptions in the skin microbiota. The enterotoxin produced by *S. aureus* may influence the expression of the T cell-related marker Foxp3,[15] thereby impairing the regulation of the response to helper T (Th) cells.[16] Foxp3 regulatory T cells (Treg) are widely distributed in human skin, and T cells can further mediate disease development in conditions such as vitiligo (eg, Th1), AD (eg, Th2/Th17), and psoriasis (eg, T17/T22)[17] (see Figure 1).

Clearly, the skin microbiome plays a crucial role in regulating immune responses. Recent studies have revealed the presence of microorganisms not only in the epidermis but also in deeper layers of the dermis and subcutaneous tissues, indicating their potential to breach the epidermis and activate downstream molecular signaling, thereby impacting homeostasis.[18] A more comprehensive understanding of the human skin microbiome and its interactions with the innate and adaptive immune systems will enhance our comprehension of these diseases and provide opportunities for new treatment modalities. This review focuses on the role of the skin microbiome in the pathogenesis of several ISDs, including AD, SD, acne, psoriasis, rosacea, DD, and malar pigment folliculitis.

Methodology

This review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] The literature search was confined to several key bibliographic databases, namely PubMed, EMBASE, Web of

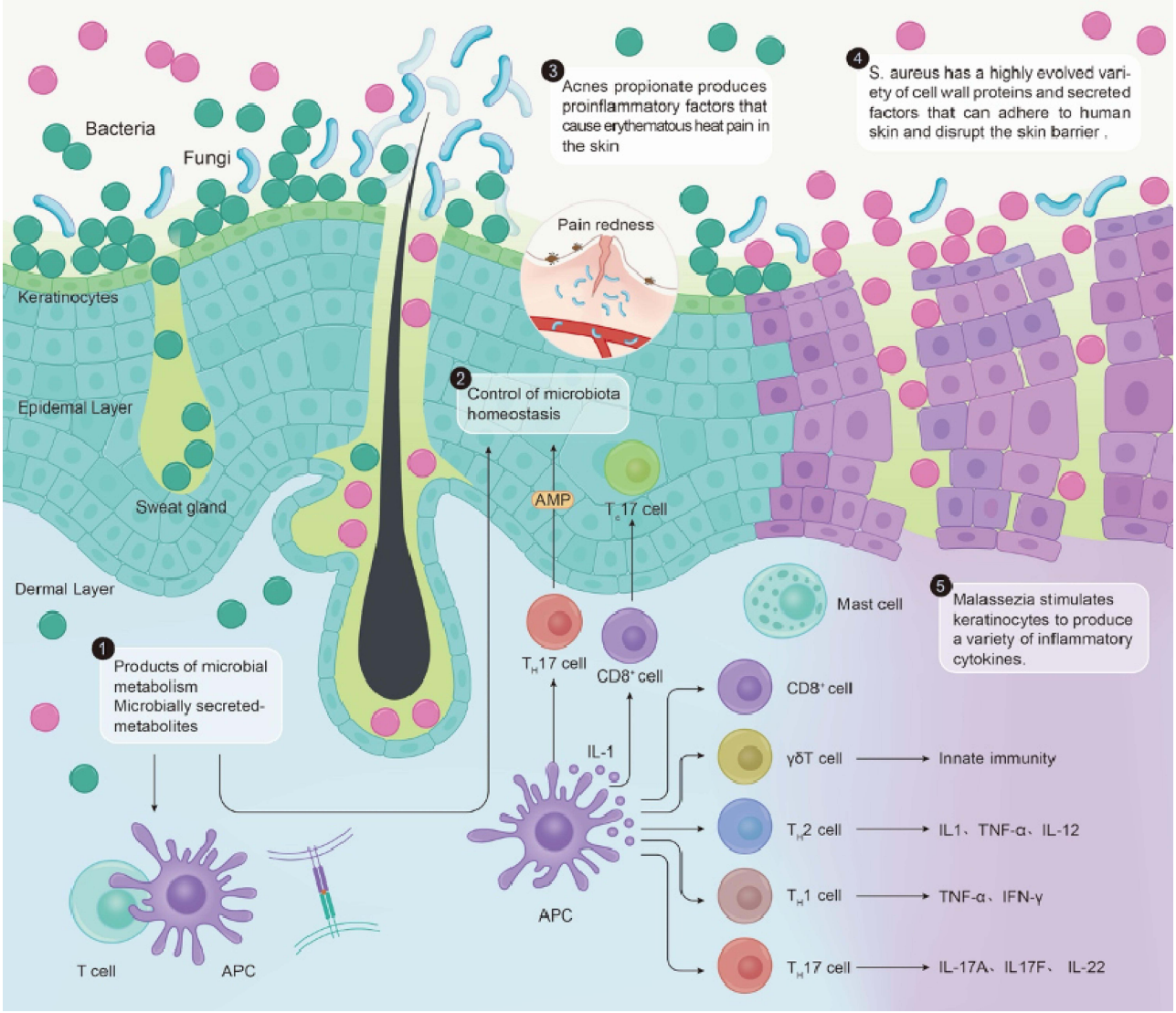

Figure 1 Crosstalk between the skin and the microbiome under conditions of pathogenic bacteria.

Science, Cochrane Library, Central, Academic Search Premier, and ScienceDirect. Two researchers (PZ, EL) independently conducted the searches using subject headings and specific keywords, encompassing terms related to bacteria, microbiota, skin microorganisms, and dermatological terms, such as "acne", "AD", "psoriasis", "rosacea", "DD", "*MF*", and "SD". Each search term was combined with its relevant keyword variants and free-text word variations. The literature review aimed to elucidate the mechanisms and implications of communication between skin bacteria and the host, as well as the impact of imbalances in the skin flora on skin health.

Inclusion criteria encompassed original studies and review articles reporting outcomes in both pediatric and adult populations, published in the English language, and focusing on the association of skin microbiota with ISDs, namely, "acne", "AD", "psoriasis", "rosacea", "DD", "MF", and "SD". Studies evaluating full-text articles, review articles, case reports, conference abstracts, and investigations concerning alterations in ISDs unrelated to the skin microbiome were excluded from the analysis. Similarly, studies utilizing culture-dependent techniques were also excluded. The search process is illustrated in Figure 2.

Microbiome Characteristics in Inflammatory Skin Diseases

With the continuous development of molecular biology and bioinformatics, techniques have significantly contributed to microbiome research. The most utilized methods for microbiome species studies today include 16S rRNA gene sequencing, metabolism, and metagenomics. 16S rRNA gene sequencing serves the purpose of investigating the

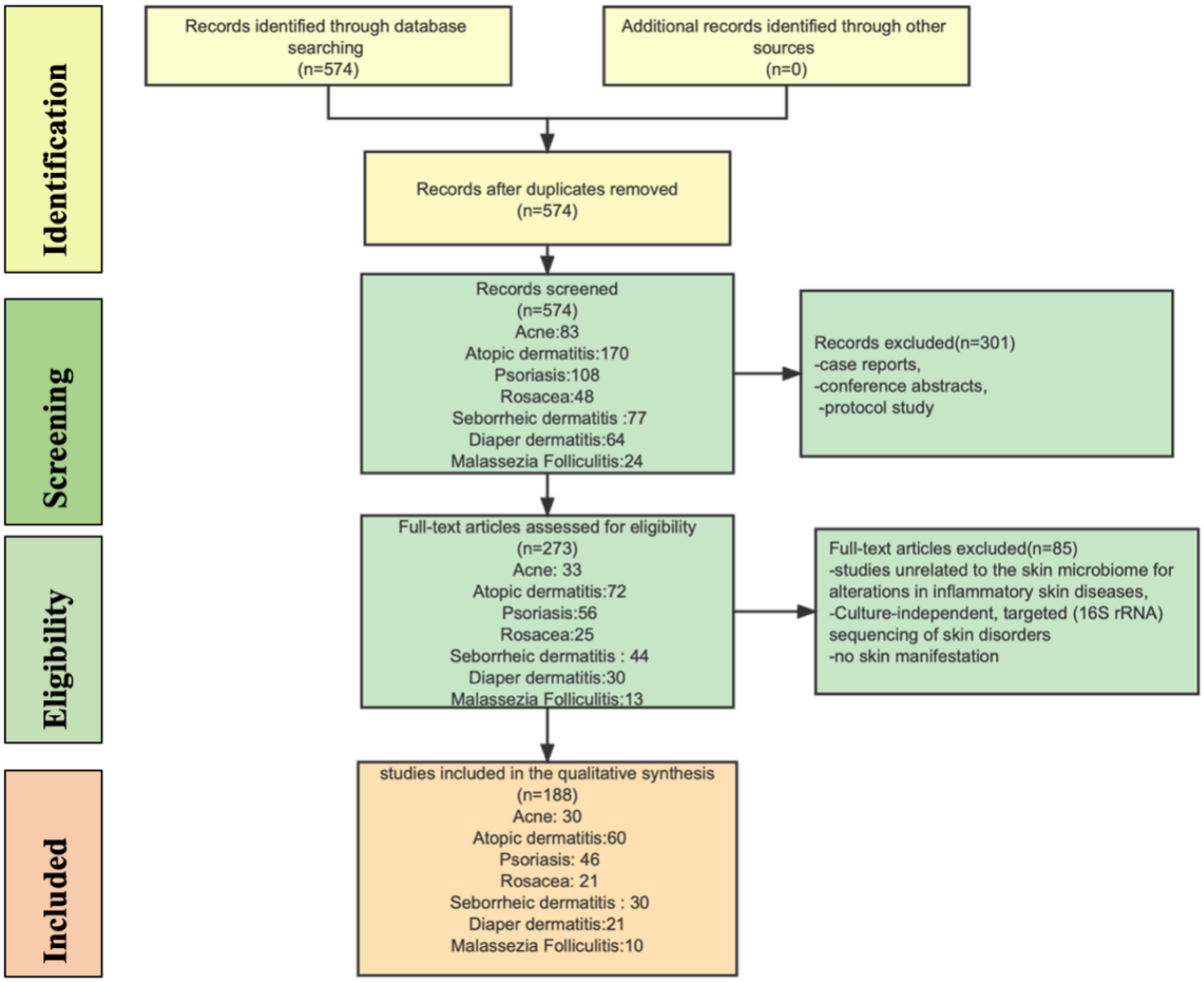

Figure 2 Flow diagram of study selection.

distinctions between species and even strains in microbiome studies. Metagenomics, on the other hand, involves the sequencing of numerous genes in a sample using modern genomic techniques without the need to isolate a specific species.[20,21] These contemporary molecular and bioinformatic techniques define the genetic diversity of microorganisms and their relationship between commensal and pathogenic microbiomes.

Recent studies have indicated associations between *S. aureus, Streptococcus pyogenes*, and *Malassezia* with disease exacerbations of psoriasis and AD. Thus, the field plays a crucial role in determining the potential microbial dysbiosis in future diseases. However, despite the recognition that disturbances in the skin microbiome could lead to pathological changes, it remains unclear whether skin microbial alterations are the "cause" or the "consequence" of disease. A definitive conclusion has not yet been reached. So far, the skin microbiome has been studied in AD, SD, psoriasis, acne, and MF (Table 1). Our compilation of information about the microbiome in common ISDs, focusing on the analysis of the microbiome's impact on human health and disease, facilitates the study of microbial composition, structure, and function, providing significant insights into immune system function and altered homeostasis.

Table 1 Characterization of the Skin Microbiota in ISDs.Note: ↑, Increase; ↓, Decrease

Disease	Microbial Alterations		Immune Dysregulation	Refs
ATOPIC DERMATITIS(AD)	↑*Staphylococcus epidermidis* ↑*Staphylococcus hemolysis* ↑*Staphylococcus spp.* ↑*Staphylococcus aureus*	↓*Cutibacterium spp.* ↓*Streptococcus spp.* ↓*Corynebacterium spp.* ↓*Propionibacterium acnes* ↓*Acinetobacter* ↓*Corynebacterium* ↓*Proteus*	↓AMP ↑IL-4,↑IL-5, ↑IL-13,↑IL-31, ↑IL-1,↑IL-12, ↑IL-22, ↑IL-6, ↑IL-8, ↑IgE, ↑TSLP, ↑TNF-α,	[22–27]
SEBORRHEIC DERMATITIS(SD)	↑*Staphylococcus spp.* ↑*Staphylococcus epidermidis* ↑*Streptococcus spp.* ↑*Pseudomonas spp.* ↑*Acinetobacter* ↑*Malassezia* ↑*Mycococcus*, ↑*Candida* ↑*Filamentous fungus spores*	↓*Cutibacterium spp.*	↑IL-1α,↑IL-1β, ↑IL-2, ↑IL-8, ↑IL-10,↑IL-12, ↑TNF-α, ↑IFN-γ	[28–32]
ROSACEA	↑*Corynebacterium kropp* ↑*Gordonia* ↑*Geobacillus*	↓*Cutibacterium acnes* ↓*Acinetobacter* ↓*Roseomonas spp.*	↑IL–10, ↑AMPs	[33]
PSORIASIS	↑*Firmicutes* ↑*Streptococcus spp.* ↑*Prevotella* ↑*Staphylococcus spp.* ↑*Staphylococcus aureus* ↑*Staphylococcus pettenkoferi* ↑*Staphylococcus sciuri* ↑*Corynebacterium kroppenstedii* ↑*Corynebacterium simulans* ↑*Neisseria spp.* ↑*Finegoldia spp.*	↓*Actinobacteria* ↓*Gordoniaceae* ↓*Staphylococcus epidermidis* ↓*Cutibacterium spp.* ↓*Staphylococcus spp.* ↓*Cutibacterium acnes* ↓*Cutibacterium granulosum* ↓*Burkholderia spp.* ↓*Lactobacilli*	↑IL-1, ↑IL-6, ↑ IL-8,↑IL17, ↑IL-12, ↑IL-23, ↑IL-22, ↑TNF- α, ↑IFN- α, ↑TGF-b, ↑iNOS,↑HSP70,	[34–37]
ACNE	↑*Firmicutes* ↑*Proteobacteria* ↑*Staphylococcus spp.*	↓*Actinobacteria* ↓*Cutibacterium spp.* ↓*Cutibacterium acnes* ↓*Cutibacterium granulosu*	↑IL-12, ↑IL-23, ↑TNF- α, ↑IFN- α	[38,39]

(*Continued*)

Table 1 (Continued).

Disease	Microbial Alterations		Immune Dysregulation	Refs
DIAPER DERMATITIS (DD)	↑*Enterococcus* ↑*Erwinia* ↑*Pseudomonas* ↑*Staphylococcus aureus*	↓*Clostridium* ↓*Actinomyces* ↓*Staphylococcus epidermidis,*	↑IL-1,↑IL-8, ↑TNF- α	[40,41]
MALASSEZIA FOLLICULITIS (MF)	↑ *Malassezia. sympodialis* ↑ *Malassezia.Restricta* ↑ *Malassezia. furfu*	-	↑IL –1α,↑IL-4, ↑IL-6, ↑IL-8, ↑IL-10, ↑IL-12 ↑TNF-α,	[42–44]

The Skin Microbiome in AD

AD is a chronic or relapsing inflammatory skin disease characterized by severe pruritus, pleomorphism, and exudation, commonly observed in infants and adolescents but may persist into adulthood or old age.[45] During the onset of AD at all ages, there is a noticeable decrease in skin microbial diversity: *Acinetobacter, Corynebacterium*, and *Proteus decrease*, while *Staphylococcus* increases (*Staphylococcus epidermidis* and *hemolytic Staphylococcus*). Notably, skin bacterial communities characterized by increased abundance of *S. aureus* exhibit reduced diversity compared to bacterial communities on healthy skin, a correlation that positively relates to disease severity.[46] Studies by Sofie et al indicated that *S. aureus* expressing variant virulence factors could induce AD-like phenotypes in mice, suggesting the potential of *S. aureus* strains to trigger flare-ups.[1] Additionally, the density of *S. aureus* is closely linked to the severity of the disease.[22,47–49]

Staphylococcus Aureus (S. Aureus)

S. aureus, a Gram-positive bacterium, can express various toxin factors and proteases. Recent research has indicated that *S. aureus* colonization is associated with AD pathogenesis, disease flares, and disease phenotypes. *S. aureus* possesses a diverse array of cell wall proteins and secreted factors that can adhere to and disrupt the skin barrier in human skin through physical, chemical, and inflammatory mechanisms.[50] The colonization of *S. aureus* on the skin of AD patients involves various factors, including changes in the epidermal barrier, increased bacterial adhesion, impaired bacterial clearance, and reduced innate immune response.

Epidermal Barrier Changes

S. aureus secretes alpha-toxin (also known as membrane attack toxin) that produces a number of proteases, including serine proteases and kallikrein (KLK6, KLK13, and KLK14).Imbalances in the activity of these proteases can dissolve the stratum corneum, leading to impaired skin barrier function.[51–54] Lipoteichoic acid (LTA), a cell wall product of *S. aureus*, causes skin barrier damage by inhibiting the expression of epidermal barrier proteins such as fibroin and loricrin.[55]

Increased Bacterial Adhesion

Studies have shown that *S. aureus* could produce several surface molecules such as clumping factors A and B, fibronectin binding protein (FNBP), and iron-regulated surface determinant protein A (ISDA) to adhere to the human stratum corneum.[56] In addition, Th2 cytokines (such as IL-4) in the skin of AD patients elevate the expression of fibronectin and fibrinogen, which may enhance the adhesion between *S. aureus* and stratum corneum.[57] Overexpression of interleukin (IL) - 4 and IL-13 on ad skin cause downregulation of cathinone (LL-37) and human β-defensin3 (HBD3).[58] LL-37 with HBD, a major component of AMPs, has direct antimicrobial activity against aureus uveitis.[53] Decreased AMP levels may increase risk factors for long-term colonization of AD skin by *S. aureus*.[58,59]

Impaired Bacterial Clearance

The average pH of the skin of AD patients is often weakly alkaline, which may reduce the levels of sphingolipids(SPL) in the stratum corneum,[60,61] which belong to the SPL class that are an important component of cell membrane structure.[62]

Low levels of expressed SPL may cause instability of cell membranes in the stratum corneum of the skin thereby leading to elevated levels of transepidermal water loss (TEWL), pH, and serum IgE, and activation of cytokines (thymus and activation of cytokines(TARC)/CCL17) and eosinophils in the AD in order to accelerate *S. aureus* colonization.Natural moisturizing factors such as filaggrin and such as filaggrin and filaggrin degradation products (FDP), play a key role in maintaining skin pH and inhibiting *S. aureus* growth in the skin.[63,64] It has also been reported that a decrease in FDP levels is associated with the severity of AD and induces strong adhesion of *S. aureus* to AD KC.[65]

Decreased Innate Immune Response

Immune response defects include the reduction of AMPs and the expression of TLR and nucleotide-binding oligomerization domain(NOD)/card receptor functional variants.[66] *S. Aureus* release a plethora of virulence factors, mainly *Staphylo*coccal *enterotoxins* (SE) characterized by super antigenic properties, such as SEA, SEB, and toxic shock syndrome toxin (TSST)-1.[67,68] *S. aureus* superantigens (SAgs) could activate many T cell clones and produce substances with strong immune responses. SAgs could trigger IgE-mediated degranulation of mast cells, thus increasing Th2 cytokines, SAgs bind to human leukocyte antigen (HLA)-DR expressed on Langerhans cells and macrophages and then stimulate the production of IL-1 and TNF-α and/or IL-12, resulting in exacerbation and recurrence of AD.[60] *S. aureus* could also induce keratinocyte apoptosis and release thymic stromal lymphopoietin (TSLP).[69] The secretion of TSLP could mediate pruritus reaction and also induce the activation of skin DCs and the recruitment of Th2 cells secreting IL-4 and IL-13.[70,71]

Malassezia

Malassezia are significant skin organisms in humans and animals, acting as both skin commensals and opportunistic pathogens. According to Sugita et al.[72] *M. globosa* and *M. restricta* are the primary skin flora in *Malassezia*-related AD. *Malasse*zia spp. considered as an aggravating factor of AD, is mainly present in the skin of head and neck patients.[73] Research also supports the idea that both topical and systemic antifungal treatments alleviate the severity of cutaneous symptoms in yeast-sensitive AD patients.[74]

Malassezia can secrete enzymes, including lipase and phospholipase, which release unsaturated free fatty acids(FFAs) from sebum lipids, triggering inflammatory responses.[75,76] Notably, tetanic acid has been shown to produce pro-inflammatory eicosanoids, such as prostaglandins, thromboxane, and leukotrienes, under the influence of phospholipase A2 (PLA2), resulting in inflammation and stratum corneum damage.[77] Additionally, studies have found that mice overexpressing PLA III exhibit skin inflammation histologically linked to AD.[78] Previous research has also identified the presence of octadecanoic acid and arachidonic acid isomers in the T lymphocyte membrane of AD patients.[79] Consequently, the formation of trans fatty acid isomers in the T cell membrane and the release of pro-inflammatory mediators in AD patients could alter T cell signal transduction activity.

Moreover, *Malassezia* can facilitate the maturation of DCs, stimulate KC to produce inflammatory cytokines (like IL-4, IL-6, IL-8, and TNF-α), induce IgE-mediated mast cell degranulation, and release leukotrienes, all contributing to the persistence of inflammatory responses.[80] However, it does not produce IL-12, which promotes the induction of Th2 responses in AD pathogenesis.[81]

Candida Albicans (C. Albicans)

C. albicans shares similarities with many pathogens in that it colonizes and invades through biofilm formation, releasing virulence factors like acid proteases and phospholipases. The biofilms assist in maintaining the dual role of fungi as commensals and pathogens by evading host immune responses, resisting antifungal treatments, and fending off competition from other organisms.[82] Phospholipases are implicated in membrane damage, adhesion, and the invasion of host cells. These enzymes hydrolyze ester links in glycerophospholipids, leading to cell lysis by targeting membrane phospholipids. Aspartyl proteases, secreted by *C. albicans* during infection, can enhance its ability to colonize and penetrate host tissues while evading the host immune system.[83] The presence of Candidalysin, produced by *C. albicans* hyphae, is critical for the development of candidiasis.[84,85] Candidalysin directly damages epithelial cell membranes by insertion, permeabilization, and the formation of pores, resulting in reduced cytoplasmic contents.[86,87]

In AD patients, *C. albicans* is more prevalent compared to healthy individuals, potentially compromising the immune system and increasing host susceptibility.[88] Javad et al found that although there was no significant difference in *Candida* species colonization between AD patients and healthy individuals, the impaired immune system of AD patients might respond to the colonization of *Candida* species and alter the disease's progression.[89,90] Studies have indicated that specific protein components of *C. albicans*, such as proteins 27, 37, 43, 46, 125, and 175 kDa, may play a crucial role in the pathogenesis of AD by stimulating the immune system and triggering immunoglobulin responses.[91]

Researchers have reported that the severity of AD is linked to the production of specific antibodies against *C. Albicans*.[92] According to Matsumura et al, AD patients had significantly higher levels of IgE antibodies to *C. albicans* compared to controls, with 85% of AD patients exhibiting high levels of IgE antibodies to *C. Albicans*.[93] In Faergemann's study, IgE anti-C. Albicans antibody levels were higher in pediatric AD patients and severe AD patients compared to mild AD and control subjects.[89]

The Skin Microbiome in Seborrheic Dermatitis

SD is a chronic and recurrent inflammatory skin condition commonly characterized by thin patches with greasy scales, typically affecting areas rich in sebaceous glands such as the scalp, face, chest, back, and body folds.[94] While the precise pathogenesis of SD/DF remains unclear, it is believed to be associated with genetic predisposition, impaired barrier function, increased sebaceous glands, and other factors.[95]

The recent advancement in scalp microbiota research has revealed SD as a polymicrobial disease arising from the ecological imbalance of fungi and bacteria.[30] Comparatively higher relative abundance of *Malassezia, Mycococcus, Candida*, and *Filamentous fungus* spores was observed in SD patients when compared to healthy individuals.[28] Notably, *Malassezia* and *Aspergillus* were identified as potential fungal biomarkers for SD, while *Staphylococcus* and *Pseudomonas* were prominent bacteria. The correlation between fungi and SD was more pronounced, particularly with an enrichment of *Malassezia*.[32,96,97]

Malassezia

Malassezia plays a significant role in the initiation of SD by engaging in the innate immune response and releasing unsaturated fatty acids and related metabolites. Interaction between *Malassezia* and epidermal cells in susceptible individuals triggers the activation of various receptors such as TLR, nod-like receptors, and C-type lectin receptors, through signaling pathways including mitogen-activated protein kinase (MPAKs), nuclear factor κ B (NF-κB), and nuclear factor of activated T cells (NFAT). This cascade leads to the production and secretion of proinflammatory cytokines and mediators, ultimately compromising the skin barrier.[98–100]

The high activity of sebum, particularly influenced by androgens, is closely associated with SD, explaining its higher prevalence among males.[101] Oleic acid, considered the primary trigger of inflammation in SD, contributes to the pathogenesis of the condition through its impact on individuals' sensitivity to this stimulating FFAs. Previous research indicated that topical application of oleic acid induced more extensive skin desquamation in SD patients compared to non-SD subjects, highlighting their heightened sensitivity to fatty acid-induced skin barrier disruption.[101,102] The lipase and phospholipase secreted by *Malassezia* decompose sebum into fatty acids on the skin surface, particularly unsaturated fatty acids such as oleic acid and arachidonic acid, leading to an inflammatory response, epidermal hyperplasia, and epithelial barrier disruption.[103] Moreover, metabolites of *M. marcescens*, such as indole derivatives, penetrate the epidermal barrier and contribute to the development of SD.[104] For instance, indole-3-formaldehyde derived from *Malassezia* binds strongly with the aryl-hydrocarbon receptor (AhR), triggering the immune process in SD.[105]

Notably, in SD, the ratio of restricted *M. marcescens/ M. globosum* increases, while M. chebula/*S. aureus* decreases.[30,106] The overgrowth and metabolism of *Malassezia* may affect the proliferation of *Staphylococcus* due to the elevated skin pH caused by unsaturated fatty acids produced by *Malassezia*. The increased skin pH provides a favorable environment for the growth of *S. aureus* and promotes the adhesion between *S. aureus* and KC. Simultaneously, symbiotic cocci secrete aspartyl protease, hindering the formation and destruction of *S. aureus* biofilm.[107,108]

The Skin Microbiome in Rosacea

Rosacea, a chronic inflammatory skin condition, is characterized by the transient or persistent erythema of the central face, often accompanied by papules and pustules. A systematic review reported by Hala Daou et al[109] suggested that the dysregulation of skin microbiota, including *Cutibacterium* acnes, *Staphylococcus epidermidis, Bacillus oleronius*, and *Demodex folliculorum*, contributes to the pathogenesis of rosacea by stimulating the innate immune system, primarily through interactions with AMPs and TLR.[110] Certain strains of skin microbiota, such as *Demodex* and *Staphylococcus epidermidis*, exhibit pathogenic effects on rosacea, while others, including *Cutibacterium* acnes and *Acinetobacter*, have protective effects. Therefore, some researchers have proposed that addressing microbiota dysbiosis could serve as a novel approach to ameliorate the dysregulation of the systemic immune system.

Staphylococcus Epidermidis

Under normal conditions, *Staphylococcus epidermidis* produces regulatory proteins, phenol solubility regulating protein-γ (PSM-γ), and phenol solubility regulating protein-δ (PSM-δ), to impede the colonization of other pathogenic microorganisms. It can also secrete lipoteichoic acid, hindering the release of anti-inflammatory factors in KC via the activation of the TLR2 signaling pathway.[111] Increased levels of the TLR2 channel have been identified in rosacea-afflicted skin, contributing to symptoms like flushing and/or blushing. With elevated TLR2 levels, the antigen of *Staphylococcus epidermidis* is increasingly recognized by TLR2. Furthermore, the rise in *Staphylococcus epidermidis* on affected skin correlates with the increase in AMPs.[112] These AMPs cleave the inactive precursor protein cathelicidin antimicrobial peptide 18 (CAP18) through serine proteases, leading to the formation of LL-37, which is likely involved in the pathogenesis of rosacea.[113]

Studies have shown that the antigen of *Staphylococcus epidermidis* induces the proliferation of peripheral blood mononuclear cells in rosacea patients and stimulates the production of cathine, matrix metalloproteinase-9 (MMP-9), tumor necrosis factor (TNF), and IL-8 by neutrophils from healthy subjects.[114] In rosacea patients, the increase in pro-inflammatory factors leads to a rise in facial skin temperature, influencing the growth and balance of microbiota and prompting *S. epidermidis* to secrete more proteins, thus establishing a vicious cycle.

Demodex

Two species, *D. folliculorum* and *D. brevis*, are typically found on the normal skin of adult humans, particularly in the sebaceous unit of the face.[115] *D. folliculorum* resides within hair follicles, while *D. brevis* is primarily present in sebaceous and meibomian glands. These Demodex species may attenuate the host's innate immune response, thereby ensuring their survival. Research indicates that *Demodex* mites express the Tn antigen, a carbohydrate coating that grants immune protection to cancer cells and parasites.[116] Additionally, *Demodex* mites influence the secretion of inflammatory cytokines such as IL-8, TNF-alpha, and the expression of TLR through interactions with corneal granulocytes.[116–118]

The activation of *Demodex* is believed to trigger the inflammatory response seen in rosacea. A meta-analysis conducted by Yin-Shuo et al found that patients with rosacea had significantly higher prevalence and severity of *Demodex* mite infestation compared to control subjects, suggesting the role of *Demodex* mites in both erythematotelangiectatic rosacea and papulopustular rosacea.[119] Ezgi et al conducted a prospective, observational case-control study involving 43 rosacea patients and 77 healthy controls, emphasizing the significant association between rosacea and *Demodex* infestation, and highlighting skin surface biopsy as a practical tool for assessing *Demodex* infestation.[118] Several studies have illustrated the involvement of *B. oleronius* proteins (83 kDa and 62 kDa) in the immune-inflammatory response of rosacea.[120–122] Furthermore, it is believed that *Demodex* mites might induce a granulomatous foreign body response through their chitin exoskeleton, subsequently leading to inflammatory changes that trigger an immune response in the host. Chitin, as part of the mite's exoskeleton, stimulates the pro-inflammatory response of KC through the TLR2 pathway, enhances protease activity, triggers immune responses, and eventually activates neutrophils and macrophages.[123,124]

Acinetobacter

In patients with rosacea, the relative abundance of Acinetobacter in facial skin is notably lower compared to that of healthy controls, and the presence of *Acinetobacter* is positively linked to the expression of anti-inflammatory factors

such as IL-10. *Acinetobacter* can induce a robust Th1 immune response and an anti-inflammatory response through immune cells and skin cells, thereby preventing allergic sensitization.[125] It is commonly understood that the Th1 immune response can bolster the host's anti-infection capabilities against microorganisms, particularly fortifying immune and defense functions against viruses and intracellular pathogens, thereby aiding in the resistance against the invasion of foreign pathogenic microorganisms. Consequently, *Acinetobacter* may assume a protective role in ISDs by intricately interacting with the immune system.[125,126]

The Skin Microbiome in Acne

The pathogenesis of acne is primarily attributed to several factors, including increased sebum production, abnormal proliferation and differentiation of KC within hair follicles, bacterial colonization, and the subsequent host inflammatory response. Microorganisms, in particular, can play a crucial role in triggering inflammatory reactions and contributing to the formation of inflammatory acne lesions, representing a key mechanism in the development of acne.

Propionibacterium Acnes (P. Acnes)

P. acnes is a microorganism that has been closely associated with acne. The pathogenicity of *P. acnes* is determined by the type of *P. acnes* strains and the balance between these strains. *P. acnes* can be divided into types I, II, and III, with ribotypes IV and V of type IA-2 and IB-1 being particularly linked to acne.[127] IA-2 and IB-1 strains induce high levels of interferon-γ (IFN-γ) and IL-17, while they elicit lower levels of IL-10, a cytokine known to mitigate inflammation by downregulating IFN-γ and IL-17. On the other hand, *P. acnes* type II induces elevated levels of IL-8 in KC.[128] Furthermore, *P. acnes* type IA and IB lead to increased levels of β-defensins in sebocytes compared to *P. acnes* type II. β-defensins in human macrophages can escalate the levels of pro-inflammatory cytokines in immune cells,[129] Additionally, β-defensin 3 disrupts cell wall biosynthesis by binding to lipid-rich regions of the cell wall, exerting antimicrobial effects.[130] Studies have confirmed that *P. acnes* can stimulate the secretion of IL-17 and IFN-γ from CD4 T cells, suggesting that acne may be mediated by Th17 cells.[131,132]

Metagenomic analysis has revealed the presence of five major microbiome types (I–V) in *P. acnes* strains.[9] Strains of ribotype 4 (RT4) and ribotype 5 (RT5) in types IV and V may carry virulence genes, which promote the adhesion of *P. acnes* to the host and induce the host immune response. Conversely, RT2 and RT6 strains are primarily enriched in healthy skin and can encode clustered regularly interspaced short palindromic repeats/CRISPR-associated protein system (CRISPR/Cas) elements, preventing these strains from acquiring invasive foreign virulence genes.[133]

Hence, it is believed that ribotypes IV and V of *P. acnes* strain IA-2 and IB-1 are closely linked to acne. Metagenomic analysis suggests that RT4 and RT5 strains of *P. acnes* type IV and V are predominant in inducing acne, while ribotype 2 (RT2) and ribotype 6 (RT6) strains appear to have a relatively protective role. An elevated adhesion and hydrolase protein has been found in IA-2 and IB-1, indicating that the proteome may be involved in specific immune responses, and a protein vaccine is anticipated to be a novel therapeutic approach for acne.

Demodex

Evidence suggests a correlation between Demodex infection and acne. Following six weeks of doxycycline treatment, studies have observed notable changes in the relative abundance of microbes on the skin surface of acne patients, including a reduction in both *P. acnes* and *Snodgrassella alvi (S. Alvi)*.[134,135] *S. alvi*, identified as a core microbiota of *Demodex* mites in rosacea patients, is implicated in the pathogenesis of acne as well[136].

Similar to its pathogenic effects in rosacea, *Demodex* or its metabolite chitin can activate the innate immune system and induce type IV hypersensitivity reactions, potentially serving as a trigger for acne development. Studies by Mumcuoglu and Akilov et al have demonstrated that *Demodex* mites can act as carriers for *B. oleronius*, a bacterium likely to play a significant role in pathogenesis.[137] *B. oleronius* proteins have been shown to stimulate neutrophil recruitment and activation.[138] The activation of neutrophils may contribute to inflammation associated with acne and can exacerbate the condition. Research has indicated that antigens from *B. oleronius* stimulate the production of MMP-9, TNF, and IL-8 by neutrophils in healthy subjects.[139,140] This inflammatory state in acne patients contributes to an increase in facial skin temperature.

Staphylococcus

Staphylococcus *epidermidis (S. Epidermidis), Staphylococcus hominis*, and coagulase-negative *Staphylococcus* can be found on the skin of both healthy individuals and those with acne.[128] Notably, the relative abundance of *Staphylococcus* epidermidis in acne-prone skin exhibited a negative correlation with *P. acnes*. Recent studies have demonstrated the inhibitory effects of *Staphylococcus epidermidis* on *P. acnes*. Christensen et al discovered a functional early secretory antigenic 6 kDa (ESAT-6) secretion system in *Staphylococcus epidermidis*, suggesting its potential role in suppressing the growth of *P. acnes* through antibacterial polymorphic toxin.[141]

Furthermore, LTA and succinic acid secreted by *S. epidermidis* were found to inhibit IL-6 induction by *S. acnes* by promoting mir-143 expression and suppressing TLR-2 expression in KC.[142–144] Intriguingly, the injection of *S. epidermidis* encapsulated glycerol into the ears of acne-bearing mice led to a significant reduction in acne growth and macrophage inflammatory protein-2 production.[145] These findings not only suggest that the increase in *S. epidermidis* coincides with clinical improvements in acne and a decrease in *P. acnes* but also highlight the potential use of *S. epidermidis* in the treatment of acne.

Malassezia

Malassezia, including *Malassezia* restrictive and *Malassezia globosa*, has been found in young acne patients.[146] *Malassezia* is a prevalent fungal organism on the skin that coexists with *P. acnes* and other bacterial species. Some researchers suggest that the potential cause of stubborn acne may be linked to *Malassezia* rather than *P. acnes*, primarily due to the lipase activity of *Malassezia*. Akasa et al demonstrated that the lipase activity of *Malassezia* was approximately 100 times higher than that of *P. acnes*.[147] *Malassezia* is a prevalent fungal organism on the skin that coexists with *P. acnes* and other bacterial species. Some researchers suggest that the potential cause of stubborn acne may be linked to *Malassezia* rather than *P. acnes*, primarily due to the lipase activity of *Malassezia*. Akasa et al demonstrated that the lipase activity of *Malassezia* was approximately 100 times higher than that of *P. acnes*.[148,149] However, the specific role of *Malassezia* in the pathogenesis of acne requires further investigation.

The Skin Microbiome in Psoriasis

Psoriasis is a common immune-mediated inflammatory skin disease characterized by the rapid proliferation of skin cells, resulting in erythema covered with scales. Recent studies have revealed a strong association between skin microbiota and psoriasis. Irmina et al found a significant decrease in microbiome alpha-diversity and beta-diversity in psoriasis-affected skin. This was characterized by reduced abundance of *Cutibacterium, Burkholderia spp*., and *Lactobacilli*, along with an increased abundance of *Corynebacterium kroppenstedii, Corynebacterium simulans, Neisseria spp*., and *Finegoldia spp*. in psoriasis skin compared to healthy skin.[150] Among these, *S. aureus* and *Streptococcus pyogenes* are highlighted as potentially playing a major role in the induction and maintenance of psoriasis. These microbes may contribute to the pathogenesis of psoriasis by stimulating the innate immune system.[151–153]

Staphylococcus Aureus (S. Aureus)

S. aureus has been identified in psoriatic lesional skin.[154] The enterotoxins produced by *S. aureus*, including SEA, SEB, SEC, SED, and TSST-1, have been demonstrated to exacerbate psoriasis, with SEB playing a prominent role in the pathogenesis of the condition.[155–157]

Research by Chang et al revealed strong Th17 polarization in mice colonized with *S. aureus*.[158] Additionally, Travers et al observed that T cells in psoriasis patients did not exhibit the expected v-βinteraction between cells and superantigen amplification. SAgs like TSST-1 activate T cells indirectly through HLA-DR molecules rather than directly. The colonization of *S. aureus* in the skin contributes to the innate immune response, including the stimulation of AMPs and the release of DCs mediators such as IL-12 and IL-23. This, in turn, expands the differentiated Th17 cell population 37. Subsequently, Th17 subsets produce pro-inflammatory mediators, such as IL-17A, TNF-α, IFN-α, and IL-22, leading to excessive proliferation of KC and infiltration of immune cells on the skin, eventually amplifying psoriatic inflammation.[159,160]

Streptococcus

Streptococcus, abundant in psoriatic skin, especially beta-hemolytic *Streptococcus*, is a clinically significant factor in triggering chronic plaque psoriasis.[161] This bacterium carries *Streptococcal M* protein and *Streptococcus* peptidoglycan, functioning as SAgs that activate T lymphocytes. *Streptococcus* peptidoglycan binds to MHC II molecules and T cell receptors, initiating a specific pathological response and releasing cytokines.[162] Moreover, *Streptococcal M* protein and pyrogenic exotoxins (A, B, and C) bind to HLA-DR molecules on dendritic cells (DCs), macrophages, and KC, activating T lymphocytes expressing inflammation-related VB family cells in psoriasis patients.[163] T cells from psoriasis patients may simultaneously react with homologous peptides of *streptococcal M* protein and keratin 6 and 17, contributing to the development of psoriasis.[164]

Propionibacterium

Alekseyenko and Hw et al observed a lower abundance of Propionibacterium in psoriatic lesions on the arms, trunk, and buttocks, with *P. acnes* being the predominant species.[36,165] *Propionibacterium* is known for its ability to produce propionic acid and free radical oxygenase (RoxP), mitigating oxidative stress, fortifying the skin barrier against external threats, and preventing skin inflammation.[166,167]

Furthermore, *P. acnes* strains have been shown to selectively induce Th17 cells with distinct phenotypes and functions in the presence of IL-2 and IL-23, contributing to immune homeostasis.[9] Chang et al identified an enrichment of *P. acnes* and *S. epidermidis* in psoriatic lesions with low *S. aureus* levels, suggesting potential antagonistic interactions between these bacteria that may influence pathogenesis.[36] Consequently, *P. acnes* strains might regulate the skin microbial community in areas such as the arms, trunk, and buttock folds by modulating the growth of specific microorganisms, thus playing a protective role in the development of psoriasis, as supported by the aforementioned findings. Nevertheless, this hypothesis requires further empirical validation.

Malassezia

Malassezia, lipid-dependent basidiomycetous yeasts, play a role in the development of skin lesions in psoriasis. Paulino et al identified dominant *Mycoplasma* species in *Malassezia* of psoriasis patients, with *Malassezia globulus (M. globosa)* and *Malassezia* following suit.[168] *Malassezia* has the capacity to up-regulate the expression of transforming growth factor-beta (TGF-β), heat shock protein 70 (HSP70), and integrin chains in human KC. This induction leads to epidermal hyperproliferation, cell migration, and contributes to the exacerbation of psoriasis.[169] HSP70 plays a dual role in immune regulation. On one hand, it enhances CD4+ and CD8+ T cell responses, regulating the adaptive immune response.[170–172] On the other hand, HSP70 engages in the innate immune response by interacting with macrophages, microglia, and DCs through TLR. This interaction activates NF-κB, leading to the upregulation of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, and IL-12), as well as the production of cpx-2 and inducible nitric oxide synthase (iNOS).[173]

Furthermore, PLA2, a key downstream component of TNF and IL-17A, plays a crucial role in the pro-inflammatory effect of the epidermis. The increased activity of cytosolic PLA2 (cPLA2) in psoriatic mast cells promotes CD1a expression in psoriasis patients, recognized by CD1a-reactive T cells, leading to IL-22 and IL-17A production.[174] Secretory PLA2 (sPLA2) enhances TLR activity by increasing intracellular uptake of poly(I:C) and phosphorylation of NF-κB and MAPKs in human KC.[175] Baroni et al demonstrated that *Mycoplasma* furfur-induced increase in IL-8 and human β-defensin 2 (HBD-2) in KC is TLR2-dependent. TLR2, when paired with TLR1 or TLR6, induces numerous pro-inflammatory cytokines, contributing to psoriasis deterioration.[176]

Candida Albicans (C. Albicans)

The presence of higher levels of *C. albicans* in oral and intestinal samples of psoriasis patients has been widely demonstrated.[177] Presently, investigations on *C. albicans* in psoriasis patients predominantly center on total peripheral blood mononuclear cells.[178] The differentiation of T lymphocytes plays a crucial role in the adaptive immune response to *C. albicans* infection. Adaptive Th1 and Th17 cell responses are believed to be essential for maintaining tissue homeostasis and mounting immune defense against *Candida* infection.[179] Th17 cells are particularly vital in antifungal defense, and defects in Th17 cells can lead to recurrent fungal infections and autoimmune diseases.[180]

Schlapbach et al reported that *C. albicans* may induce an increase in IL-9 in psoriasis lesions.[181] Jesús-Gil et al described heightened responses of CLA+ CD4+ T cells to IL-9, IL-17A, and IFN-γ following *C. albicans* activation in

psoriasis patients compared to healthy subjects. This increased induction by *C. albicans* may contribute to the IL-17/Th17 loop that perpetuates psoriasis.[182,183]

The Skin Microbiome in Diaper Dermatitis

DD is a prevalent form of irritant contact dermatitis affecting infants and young children. Factors such as the conducive environment under the diaper, skin damage by fecal enzymes, and other irritants contribute to the onset of DD. The condition is triggered by exposure to unfavorable fecal enzymes, friction, and prolonged contact with urine and feces, leading to elevated skin pH.[184]

Several pertinent studies have observed higher overall skin bacterial richness and diversity in children with DD compared to healthy groups. In the DD group, there was a notable increase in the richness of *Enterococcus, Erwinia*, and *Pseudomonas*, while the levels of *Clostridium* and *Actinomyces* were significantly lower than those in healthy children.[41] Importantly, DD is characterized by a deficiency in beneficial bacterial strains, including *Staphylococcus epidermidis, Bifidobacterium longum, Clostridium butyricum*, and *Lactobacillus ruminis*.[41] Based on current research, *S. aureus* and *C. albicans* are identified as key players in the development of DD.[185,186]

Staphylococcus Aureus (S. Aureus)

Current studies suggest that *S. aureus* plays a dominant role in DD.[187,188] The colonization of *S. aureus* in children with DD is associated with variations in skin pH and fecal enzymes. Elevated pH disrupts the acidic protective layer of the epidermis, crucial for innate antimicrobial protection against pathogenic yeasts and bacteria. This disruption creates a conducive environment for *S. aureus* colonization, exacerbated by ammonia-induced alkalinization activating fecal enzymes like lipase and trypsin, causing irritation and compromising the skin barrier.[189]

During early childhood, when innate immunity prevails, interleukin-1 receptor (IL-1R) and TLR family members signal through myeloid differentiation primary response 88 (MyD88) to induce neutrophil protective responses to *S. aureus* skin infection. MyD88 then interacts with interleukin-1 receptor-associated kinase 4 (irak4), activating TNFR-associated factor 6 (TRAF6) and initiating NF-κB and MAPK signaling pathways, leading to the transcription of pro-inflammatory genes (such as TNF, IL-6, and C-X-C motif ligand 8(CXCL8)).[190,191] The inflammatory response in buttock skin is marked by the release of proinflammatory mediators due to *S. aureus*, resulting in features like neutrophil abscess formation. *S. aureus* infection typically leads to increased levels of IL-1β, TNF-α, IL-6, and IL-8.[188] The secretion of staphylococcal enterotoxin A (SEA) by *S. aureus* contributes to skin redness and DD-like lesions and may contribute to low-grade fever.[192]

Notably, in severe DD skin lesions, *S. aureus* is the predominant *Staphylococcus* species, while the abundance of *S. epidermidis* decreases with increasing DD severity. Zheng et al suggest that *S. epidermidis*, employed as a skin probiotic, could be beneficial in treating and preventing DD. Their observations indicate that after DD improvement with emollient treatment, the abundances of dominant species *S. epidermidis* and *S. haemolyticus* in buttock skin increased compared to pre-treatment levels and returned to normal levels.[41]

Candida Albicans (C. Albicans)

C. albicans emerges as the predominant species in the genital, perianal, and trigone regions, likely owing to the favorable warmth and moisture in these areas, facilitating the penetration of the cuticle by *Candida* species.[193] The elevated levels of heat, humidity, and carbon dioxide further heighten the skin's susceptibility to *Candida* spore infection in these regions.[194]

Neonatal skin, particularly in preterm infants, has an increased likelihood of developing disseminated cutaneous and systemic *Candida* infections.[195] Congenital candidiasis infections in preterm infants manifest as large areas of erythema, papules, pustules, and diffuse "burn-like" erythema with excoriation.[196] The initiation of skin inflammation and erythema in DD is primarily attributed to the release of proinflammatory cytokines IL-1αand TNF-α. Infants using diapers exhibit higher skin pH, increased hydration, and elevated concentrations of IL-1αand IL-8 compared to those not using diapers, highlighting the influence of diaper usage on skin conditions.[197,198] IL-αrecognized as a major driver of inflammation in DD. During *C. albicans* infection, cytokines such asIL-6, TNF-α, IL-12, IFN-γand IL-17 typically emerge in the initial stages of skin infection.

The Skin Microbiome in *Malassezia Folliculitis* (MF)

MF manifests as an intensely pruritic, follicular, papulopustular eruption, commonly appearing on the upper back, chest, and shoulders, particularly affecting adolescents, possibly linked to increased sebaceous gland activity.[199,200] Existing literature suggests that an imbalance between *Malassezia* and its host may be a key factor in the development of MF.[42]

In MF lesion samples, the most frequently identified species were *M. globosa* (69.4%), followed by *M. sympodialis, M. restricta*, and *M. furfur*.[201] Culture method analysis by Akaza et al revealed that dominant species recovered from MF lesions were *M. globosa* and *M. sympodialis*, while non-culture method analysis identified *M. restricta, M. globosa*, and *M. sympodialis*.[43]

Several mechanisms may contribute to the inflammatory component of MF induced by *Malassezia*. One mechanism involves the induction of inflammatory cytokine production by KC via TLR 2.[202] These inflammatory cytokines include IL-α, IL-6, IL-8, IL-12, TNF-α, and the anti-inflammatory cytokines are IL-4 and IL-10. *Malassezia* can activate the complement cascade through classical and alternative pathways.[199] Another potential mechanism involves *Malassezia*'s lipase and phospholipase hydrolyzing triglycerides into FFAs, compromising epithelial barrier function. This impairment may lead to increased sensitivity to cross-reactive allergens and immune system irritancy.[202,203]

Treatment Approaches

Current research on skin diseases emphasizes the role of skin microbiota, highlighting its impact on health. Studies indicate that dysregulation of skin microbiota can lead to the translocation of bacteria from the gut and skin into the bloodstream. Bacteria entering the bloodstream act as drivers for chronic systemic inflammation, establishing a connection between the skin and gut microbiota through the Gut-Brain-Skin Axis. Consequently, there is a growing recognition of the theory that repairing skin barriers should consider the perspective of skin microbiota.

Our focus extends to exploring the relationships between various treatment approaches, such as the use of probiotics, transplantation of coagulase-negative staphylococci (CONS) flora, AMPs, and microorganisms. We aim to understand the underlying mechanisms of these treatments in comparison to conventional approaches. This research avenue holds promise for advancing our understanding of skin diseases and developing novel therapeutic strategies.

Intake of Probiotics and Prebiotics

The consumption of probiotics not only addresses disorders in intestinal flora but also enhances mucus production and the function of epithelial tight junctions, thereby promoting barrier integrity. Additionally, probiotics contribute to the secretion of various metabolites and neurotransmitters, such as SCFAs, phenols, 5-hydroxytryptamine, and tryptophan. These compounds influence intestinal mucosal permeability, entering the circulatory system and affecting skin barrier function. Probiotics play a role in inducing the production of anti-inflammatory cytokine IL-10 in peripheral regulatory T lymphocytes and stimulating the secretion of hypothalamic hormones, thereby regulating the immune state of the skin.[204–206] Currently, probiotics have demonstrated therapeutic potential in various inflammatory diseases, including AD, acne vulgaris, psoriasis, SD, and more.[207–209]

Antibacterial Activity

The decline in the levels of AMPs exacerbates the colonization of pathogenic microorganisms, increasing the susceptibility to severe skin, multi-organ, and systemic infections in individuals with AD. AMP therapy holds the potential to alleviate skin inflammation and restore the epidermal barrier by enhancing the innate immune system. Omiganan (OMN), classified as an AMP, exhibits broad-spectrum antibacterial and antibiofilm activities.[210] OMN has garnered considerable attention for its application in the treatment of various inflammatory conditions, including acne vulgaris, rosacea, condyloma acuminatum, vulvar candidiasis, among others.[211,212]

Cons

CONS, comprising *Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus haemolyticus*, and *Staphylococcus capitis*, among other common isolates, are typical skin commensals. Recent research indicates that skin-residing CONS exhibit an anti-colonization effect through the production of AMPs and competitive antagonism against invading pathogens. This action

primes the skin's immune system, enhancing the activity of the complement system (IL-1 levels) to restrict pathogen colonization.[213–215]

The antibacterial capacity of the CONS bacterial community, primarily dominated by *S. epidermidis* and *S. hominis*, has been closely linked to the colonization of *S. aureus*.[216] For instance, PSM expressed by *S. epidermidis* has demonstrated the ability to eliminate *S. aureus*.[217] Serine proteases secreted by a subset of *S. epidermidis* have been found to inhibit biofilm formation and nasal colonization by the human pathogen *S. Aureus*.[218,219] Additionally, Myles et al discovered that the transplantation of healthy human mucoid Roseomonas mucosa via Lysophosphatidylcholines (LPC) effectively alleviated AD by repairing the barrier function and activating innate immunity.[216]

Transplantation of CONS appears to restore the homeostatic balance of the skin microbial community more effectively than antibiotic therapy. This is because the nonspecific antimicrobial effects of drug-derived antibiotics are likely to eliminate protective strains such as CONS, thereby increasing the risk of colonization by harmful strains.

Conclusion

Our investigation into the common flora and pathogenic mechanisms of ISDs underscores the intricate and dynamic nature of the skin microbiome. In extrapolating the participation of identical flora in potential pathogenesis across diverse inflammatory diseases (Tables 2 and 3), we have identified several key mechanisms through which the flora interacts with the host. These include:(1) Formation of biofilms: Biofilm formation counters antibiotic resistance and enhances organism colonization.(2) Evasion of host immune system: *S. aureus* inhibits neutrophil activation, while *S. epidermidis* exopolymerization prevents antibody recognition, evading neutrophil ingestion and killing. (3)

Table 2 Role of Staphylococcal SAgs and *Candida Albicans* in Inflammatory Skin Diseases

Microorganism	Virulence Factors	Possible role in AD	Possible role in Psoriasis	Possible role in DD	Refs
Staphylococcus aureus	α-toxin	Keratinocyte membrane damage / lysis that erodes epidermal barrier integrity			[220,221]
	d-Toxin	Stimulates mast cell degranulation and synergizes with IgE to induce allergic skin inflammation			[222]
	Protein A	Proinflammatory. Binds to TNFR-1 on keratinocytes			[223,224]
	Clumping factor B	Adherence of the stratum corneum to corneocytes promotes colonization by S. aureus			[225]
	Protease	Facilitate dissolution of the stratum corneum			[226]
	Phenol-soluble Modulins (PSM)	Stimulates keratinocyte production of Il-36, IL-17A, and Th17 inflammation, triggering AD associated skin pro-inflammatory responses.	/	/	[227,228]
	Staphylococcal SAgs (SEA, SEB, SEC, TSST-1)	Triggers B cell expansion of keratinocytes, APC mediated T cell activation, mast cell degranulation. Causes superantigen responses to produce IL-1, TNF-α Etc. proinflammatory factors. Induces local erythema and dermatitis.Sometimes causes disease flare.	DCs are stimulated to release IL-12 and IL-23, differentiate into Th17 cell populations, and produce pro-inflammatory mediators, such as IL-17, TNF- α, IFN- α And IL-22.	SEAcauses skin redness and damage to DD like skin lesions and may contribute to low-grade fever	[1,70,71]

(*Continued*)

Table 2 (Continued).

Microorganism	Virulence Factors	Possible role in AD	Possible role in Psoriasis	Possible role in DD	Refs
Candida albicans	Phospholipase	Associated with membrane damage, adhesion, and penetration of host cells. Hydrolyzes one or more ester linkages in glycerophospholipids. Resulting in cell lysis.			[83]
	Aspartyl proteases	Enhances the ability of an organism to colonize and penetrate host tissues as well as to evade the host immune system.			[84,85]
	Biomembrane	Evasion of host immune mechanisms, resistance to antifungal therapy.			[82]
	Candidalysin	Disruption of the epithelial membrane by embedding, permeabilizing, and creating holes leads to weakening of the cytoplasmic contents.			[86,87]
	Candida specific antibodies	High levels of IgE	High levels of IgA	/	[93,183]
	Protein compounds of *C. albicans*	Proteins 27, 37, 43, 46, 125, and 175 kDa, which stimulate the ad immune system and immunoglobulin response.	/	/	[91]

Table 3 Role of *Malassezia* in Inflammatory Skin Diseases

Diseases	Possible Role of *Malassezia* in Inflammatory Skin Diseases.	Refs
AD	Lipases and phospholipases are produced that release unsaturated free fatty acids from sebum to initiate inflammatory responses. Keratinocytes are stimulated to produce inflammatory cytokines (such as IL-4, IL-6, IL-8, and TNF- α), Induces IgE mediated mast cell degranulation, and the release of leukotrienes,	[77] [80]
SD	Stimulates IL-8 secretion and inhibits IL-1 secretion. Lipases and phospholipases are produced that release unsaturated free fatty acids from sebum to initiate inflammatory responses. Generation of tryptophan metabolites like indole derivatives (indole-3-formaldehyde) triggers SD immune response.	[229] [230]
Ance	Lipases and phospholipases are produced that release unsaturated free fatty acids from sebum to initiate inflammatory responses. Abnormal keratinization affecting the hair follicle duct, chemotactic for polymorphonuclear neutrophils and promoting the secretion of proinflammatory cytokines by keratinocytes and monocytes.	[149] [148]
Psoriasis	Upregulation of TNF-α, IL-1, IL-6, IL-8, and IL-12. Lipases and phospholipases are produced that release unsaturated free fatty acids from sebum to initiate inflammatory responses. Upregulated expression of heat shock protein 70 (HSP70).Involved in the innate immune response leading to NF- κ B activation, with release of pro-inflammatory cytokines. Upregulates CD4 + and CD8 + T cell responses, and modulates adaptive immune responses.	[173] [171] [172]
MF	Lipases and phospholipases are produced that release unsaturated free fatty acids from sebum to initiate inflammatory responses. Upregulation of IL- α, IL-6, IL-8, IL-12, TNF-α and the anti-inflammatory cytokines IL-4 and IL-10	[199]

Secretion of virulence Factors: Production of lipases and proteases increases protein hydrolysis, lysing ruptured cells, penetrating host tissues, and disrupting the skin barrier.(4) Interactions with cutaneous immune cells: These interactions induce the production of pro-inflammatory cytokines, triggering an inflammatory response.

Recent studies highlight the impact of different delivery modes on early childhood microbiota characteristics, influencing host-microbe homeostasis. The early stages of life are crucial for generating appropriate immune responses to microbes, presenting an intervention opportunity for microbiome modulation. Specific bacterial strains can either protect skin health or contribute to disease development. Exploring the potential of commensal bacteria for treating inflammatory skin damage, especially by focusing on specific bacterial strains, reveals the potential of enhancing microbiome therapy through community dynamics. However, the variability of beneficial and harmful strains across diseases requires further exploration, and the full impact has yet to be elucidated.

Looking ahead, skin microbiome-specific targeted therapy presents a novel approach for treating ISDs. To unravel the intricate mechanisms of microbe-skin immunity interaction, multi-omics approaches, including meta-transcriptomics, metagenomics, and metabolomics, are essential. These techniques will unveil the functional and gene expression roles of microbes in skin health and disease, paving the way for innovative therapeutic strategies.

Microorganisms, such as fungi and bacteria, colonize the skin surface and inhabit various skin appendages, including hair follicles, sebaceous glands, and sweat glands. Skin-residing microorganisms facilitate the production of AMPs by KC and the generation of complement by antigen-presenting cells (APCs) and other innate immune mediators. These components interact with the host, establishing a functional immune response and preventing the proliferation of pathogenic microorganisms. Dysfunctions in the skin microbiota and bacterial-induced skin barrier damage activate downstream molecular signals, triggering chronic inflammatory responses. These responses can be characterized as follows:1) Stimulation of AMPs leading to mast cell degranulation, activation of DCs for T cell binding, resulting in the proliferation and polarization of T cells (Th1/Th2 and Th17/Treg imbalance).2) Release of toxin factors, including Staphylococcal enterotoxin A (SEA), Staphylococcal enterotoxin B (SEB), Staphylococcal enterotoxin C (SEC), and α-toxin-induced cell membrane lysis.3) Hsp70 activation via Toll-like receptor (TLR) pathways causing overexpression of NF-κB, which subsequently promotes the release of inflammatory cytokines, triggering cutaneous inflammatory responses.

Abbreviations

AD, atopic dermatitis; aryl-hydrocarbon receptor; AMP, antimicrobial peptides; AMPS, antimicrobial peptide; APCs, antigen-presenting cells; C. albicans, Candida albicans; CAP18, cathelicidin antimicrobial peptide 18; CGRP, calcitonin gene-related peptide; CLFA, clumping factors A; CLFB, clumping factors B; CLR, C-type lectin receptor; CONS, coagulase-negative staphylococci; cPLA2, cytosolic PLA2; CRISPR/Cas, CRISPR-associated proteins system; CXCL8, C-X-C motif ligand 8; DC, dendritic cell; DCs, dendritic cells; DD, Diaper Dermatitis; *DF*, dandruff; ESAT-6, early secretory antigenic 6; FDP, filaggrin degradation products; FFA, free fatty acid; FNBP, fibronectin binding protein; HBD, humanβ- defensin; HBD-2, humanβ-defensin 2; HBD-3, humanβ-defensin 3; HLA, human leukocyte antigen; HSP70, heat shock protein 70; IFN-γ, interferon-gamma; IL, interleukin; IL-23, interleukin-23; iNOS, inducible nitric oxide synthase; irak4, interleukin-1 receptor-associated kinase 4; ISDA, iron-regulated surface determinant protein A; ISDs, inflammatory skin diseases; KC, keratinocytes; LPC, Lys phosphatidylcholines; LTA, Lipoteichoic acid; MF, Malassezia folliculitis; M. globose, Malassezia. globosa; M. furfur, Malassezia. furfur; M. restricta, Malassezia. restricta; M. sympodialis, Malassezia. sympodialis; MMP-9, matrix metallo proteinase-9; MPAKs, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response 88; NFAT, activated T cells; NF-κB, nuclear factor κ B; NOD, nucleotide-binding oligomerization domain; OMN, Omiganan; P. acnes, Propionibacterium acnes; PLA2, phospholipase A2; PSM-γ, phenol solubility regulating protein-γ; PSM-δ, phenol solubility regulating protein-δ; Roxp, radical oxygenase; RT2, ribotype 2; RT4, ribotype 4; RT5, ribotype 5; SAgs, Staphylococcus aureus superantigens; S. aureus, Staphylococcus aureus; SCFAs, short-chain fatty acids; SD, Seborrheic dermatitis; SE, Staphylococcal enterotoxins; SEA, Staphylococcal enterotoxin A; SEB, Staphylococcal enterotoxin B; SEC, Staphylococcal enterotoxin C; SPL, sphingolipids; S. Alvi, Snodgrassella alvi; S. Epidermidis, Staphylococcus epidermidis; TARC, thymus and activation of cytokines; TRAF6, TNFR-associated factor 6; TEWL, transepidermal water loss; TGF-β, transforming growth factor-beta; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; TSST, toxic shock syndrome toxin. (See Table 4).

Table 4 Abbreviations

Abbreviation	Full Name
AD	Atopic dermatitis
AhR	Aryl-hydrocarbon receptor
AMP	Antimicrobial peptides
AMPS	Antimicrobial peptides
APCs	Antigen-presenting cells
C. albicans	*Candida albicans*
CAP18	Cathelicidin antimicrobial peptide 18
CGRP	Calcitonin gene-related peptide
CLFA	Clumping factors A
CLFB	Clumping factors B
CLR	C-type lectin receptor
CONS	Coagulase-negative staphylococci
cPLA2	Cytosolic PLA2
CRISPR/Cas	CRISPR-associated proteins system
CXCL8	C-X-C motif ligand 8
DC	Dendritic cell
DCs	Dendritic cells
DD	Diaper Dermatitis
DF	Dandruff
ESAT-6	Early secretory antigenic 6
FDP	Filaggrin degradation products
FFA	Free fatty acid
FNBP	Fibronectin binding protein
HBD	Humanβ- defensin
HBD-2	Humanβ-defensin 2
HBD-3	Humanβ-defensin 3
HLA	Human leukocyte antigen
HSP70	heat shock protein 70
IFN-γ	Interferon-gamma
IL	Interleukin
IL-23	Interleukin-23
iNOS	Inducible nitric oxide synthase
irak4	Interleukin-1 receptor-associated kinase 4
ISDA	Iron-regulated surface determinant protein A
ISDs	Inflammatory skin diseases
KC	Keratinocytes
LPC	Lysophosphatidylcholines
LTA	Lipoteichoic acid
MF	*Malassezia folliculitis*
M. globosa	*Malassezia. globosa*
M. furfur	*Malassezia. furfur*
M. restricta	*Malassezia. restricta*
M. sympodialis	*Malassezia. sympodialis*
MMP-9	Matrix metallo proteinase-9
MPAKs	Mitogen-activated protein kinase
MyD88	Myeloid differentiation primary response 88
NFAT	Activated T cells
NF-κB	Nuclear factor κ B
NOD	Nucleotide-binding oligomerization domain
OMN	Omiganan
P. acnes	*Propionibacterium acnes*

(*Continued*)

Table 4 (Continued).

Abbreviation	Full Name
PLA2	Phospholipase A2
PSM-γ	Phenol solubility regulating protein-γ
PSM-δ	Phenol solubility regulating protein-δ
Roxp	Radical oxygenase
RT2	Ribotype 2
RT4	Ribotype 4
RT5	Ribotype 5
SAgs	Staphylococcus aureus superantigens
S. aureus	*Staphylococcus aureus*
SCFAs	Short-chain fatty acids
SD	Seborrheic dermatitis
SE	Staphylococcal enterotoxins
SEA	Staphylococcal enterotoxin A
SEB	Staphylococcal enterotoxin B
SEC	Staphylococcal enterotoxin C
SPL	Sphingolipids
S. Alvi	*Snodgrassella alvi*
S. Epidermidis	*Staphylococcus epidermidis*
TARC	Thymus and activation of cytokines
TRAF6	TNFR-associated factor 6
TEWL	Transepidermal water loss
TGF-β	Transforming growth factor-beta
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
TSST	Toxic shock syndrome toxin

Data Sharing Statement

The analyzed data in this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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All authors declare no conflicts of interest in this work.

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