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Atopic Dermatitis and Holobiome: a review on molecular mechanisms and Host-Microbiota Interactions

Gianluca Mirra[1], Bianca Gragnoli[2], Francesca Cipriani[3], Pasquale Comberiati[2], Giampaolo Ricci[4], Elena Galli[1], Nunzia Maiello[5]

[1] Pediatric Allergology Unit, Department of Pediatric Medicine, S. Pietro Hospital Fatebenefratelli, Roma, Italy; [2] Department of Clinical and Experimental Medicine, Section of Paediatrics, University of Pisa, Pisa, Italy; [3] Primary Care Pediatrics, AUSL Bologna, Italy; [4] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; [5] Department of Woman, Child and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

ABSTRACT

Atopic dermatitis is a multifactorial cutaneous chronic inflammatory disease. A crucial role in its pathogenesis is played by interaction between genomes of the host and skin microbiota, which is the basis of the holobiome theory. Genetic and environmental factors influence the microbial composition of skin. Alterations in filaggrin compromise the integrity of the skin barrier, alter skin's hydration status and pH, and allow for increased colonization by *S. aureus*. Th2-mediated inflammation reduces antimicrobial peptides, lipid synthesis and epidermal differentiation, further worsening the condition. Impaired skin flora differentiation guide to excessive proliferation of *S. aureus*, whose toxins degrade skin proteins and form a protective layer around itself. On the other hand, common commensal bacteria produce immunoregulatory substances and inhibit the proliferation of *S. aureus*. Other factors, such as lipid composition and microbial communication signals, modulate the interaction between skin and microbes. Understanding atopic dermatitis in the context of the holobiome could facilitate the development of targeted therapies aimed at restoring microbial balance and skin barrier function.

KEYWORDS: holobiome, atopic dermatitis, skin microbiome

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CORRESPONDENCE

Gianluca Mirra
gianlucamirra1@gmail.com

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INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disease with multifactorial pathogenesis, characterized by alterations in integrity of the skin barrier, immune response, and composition of cutaneous microbiota [1] (Fig. 1). Increasing evidence indicates that the composition and activity of microorganisms colonizing the skin are crucial for the onset of AD. In this context, the holobiome theory – already well established in plant and invertebrate biology – emphasizes the importance of the interaction between host genetics and colonizing microorganisms [2]. This review discusses current knowledge on the holobiome in AD, focusing on its complex interplay with pathogenetic factors for AD, such as epidermal barrier dysfunction, Th2-mediated inflammation, microbial dysbiosis, and *Staphylococcus aureus* colonization. Host-microbe interactions are critically examined.

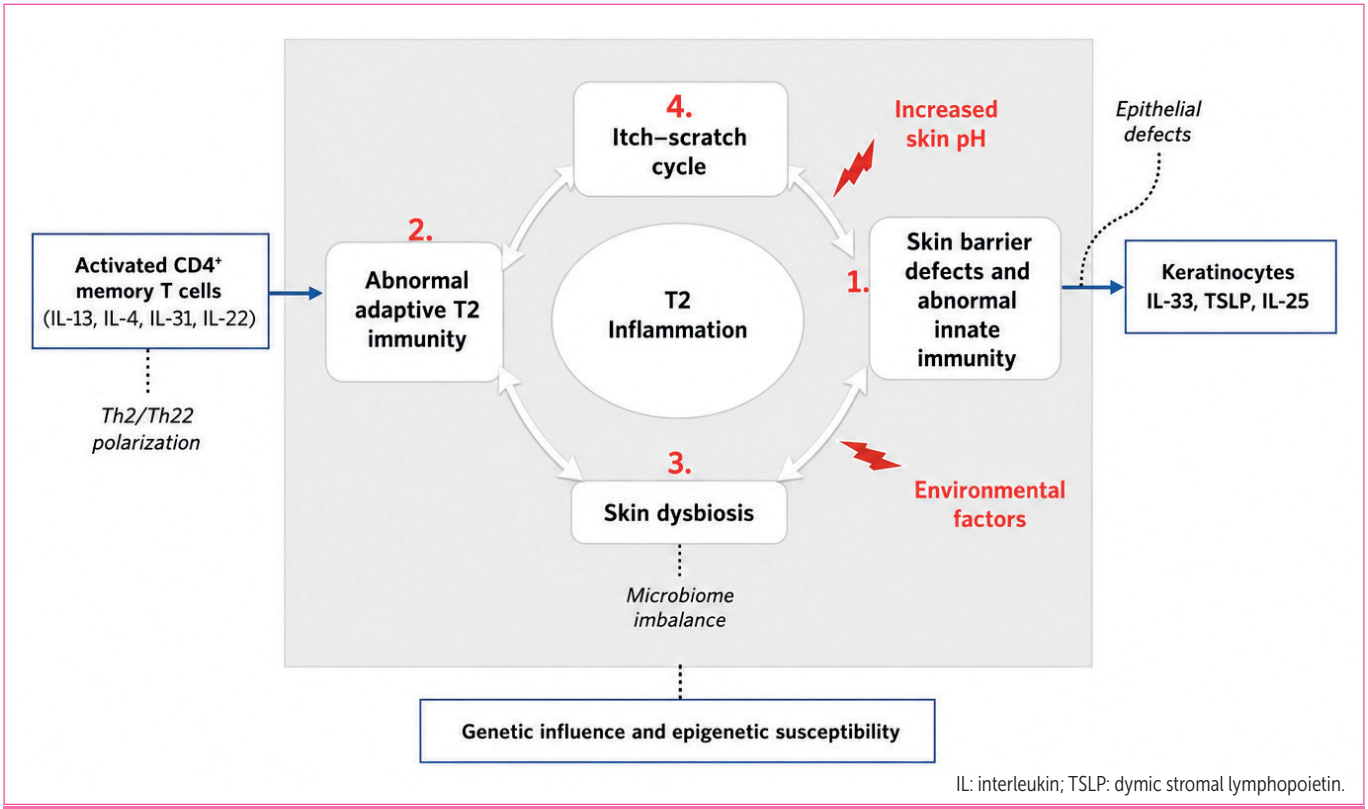


FIGURE 1. Atopic dermatitis pathogenesis: interplay of genetic, immunologic, and environmental factors. AD arises from a complex interaction between genetic predisposition, immune dysregulation, epidermal barrier dysfunction, and environmental influences. The cycle highlights four key pathogenetic steps that perpetuate chronic inflammation and pruritus, leading to recurrent flares and disease chronicity.

HOST FACTORS AND SKIN BARRIER DYSFUNCTION

Epidermal Barrier Integrity in Atopic Dermatitis

The skin barrier is a complex and highly specialized structure, and its physiology, microenvironment composition and diversity is strongly regulated by host characteristics such as sex, age, body mass index, genetics, lifestyle and environmental exposures. In particular, the effect of genetics on the skin microbiota has been evaluated in recent studies in three different microenvironments across two German population cohorts [3], identifying 23 genomic loci harboring 30 genes potentially involved in innate immune responses, environmental sensing, cellular differentiation, proliferation, and fibroblast activity. Commensal microorganisms, such as *Staphylococcus epidermidis,* can regulate host gene expression and epithelial homeostasis, supporting the concept of a dynamic host-microbe interaction. Various additional skin factors, including water content, lipids, pH, and bacterial metabolites, further influence the characteristics of skin microbiota [4] and are affected by endogenous and exogenous factors (*e.g.*, antibiotic or soap use).

Skin consists of a microbial, physical, biochemical, immunological, and neurosensory barrier separating the internal from external environment [5]. Keratinocytes are primarily responsible for the stability and immunology of the epithelial barrier. These cells are capable of initiating a type 2 immune response (Fig. 2). Skin is not an impermeable barrier to microbes; however, only selected bacteria can translocate across the epithelial barrier. This penetration is tightly regulated by specific elements, particularly cathelicidin and filaggrin (FLG) [6].

FLG, a key structural protein of the stratum corneum, plays a central role in AD pathogenesis [7]. The complex interaction among stratum corneum pH, filaggrin proteolysis, natural moisturizing factor (NMF) production and the appropriate ratio of intrinsic lipids determines skin barrier function [8].

Patients with AD may exhibit genetic and epigenetic abnormalities that alter the expression of FLG, tight junctions, epidermal lipids, and protease activity[9].

FLG and FLG2, together with loricrin (LOR) and involucrin (IVL), are located on chromosome 1q21.3 and, along with the S100A7 gene

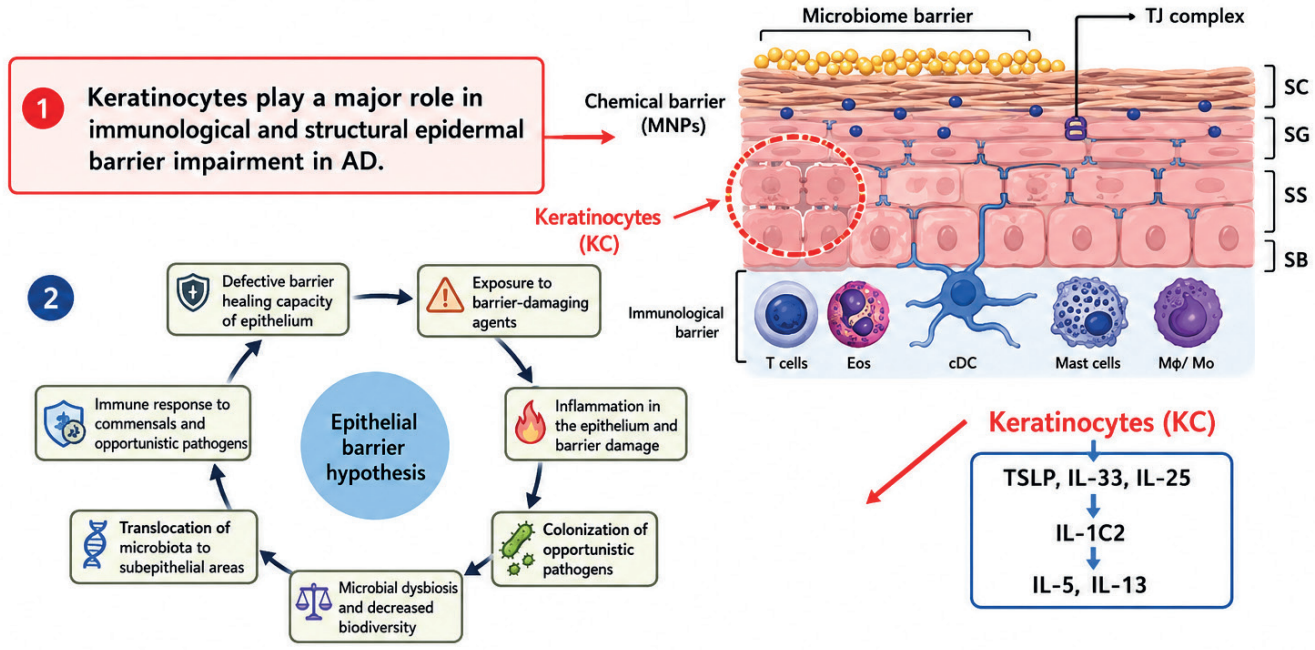


FIGURE 2. The central role of keratinocytes in epithelial barrier dysfunction in atopic dermatitis.
1) Keratinocytes are key players both immunological and structural barrier impairment. They sense environmental insults (*e.g.,* chemical agents and micro/nanoplastics), lose tight junction (TJ) integrity, and interact with immune cells within the local microenvironment. Activated keratinocytes release epithelial cytokines and alarmins (TSLP, IL-33, IL-25), which amplify type 2-skewed inflammation via IL-1C2 and promote downstream IL-5 and IL-13 responses. 2) The epithelial barrier hypothesis. Barrier dysfunction initiates a self-perpetuating vicious cycle involving inflammation, impaired healing, microbial dysbiosis, pathogen colonization, and immune activation.

cluster, constitute a major part of the epidermal differentiation complex. Mutations in FLG cause barrier defects with altered hydration and pH of the stratum corneum [10].

Water availability is essential for microbial growth on the skin. This is defined as water activity (aw), ranging from 0 (no free water) to 1.0 (all water molecules are free) and significantly affects microbial growth: *S. aureus* can grow at aw as low as 0.83, *S. epidermidis* is less tolerant (unable to grow below aw 0.87), and *Pseudomonas fluorescens* cannot grow at aw < 0.97. Thus, dry skin – a hallmark of AD – favors the growth of potentially invasive staphylococci while inhibiting commensal organisms [11].

In addition to direct FLG mutations, Th2 cytokines IL-4, IL-13, and IL-31 can suppress FLG expression and/or interfere with keratinocyte differentiation [12], downregulate TH1 (interferon gamma) and TH17 (IL-17) – dependent skin defense mechanisms, affect NMF composition and function, and suppress antimicrobial peptide (AMP) production such as cathelicidin and β-defensins. [13] *S. aureus* stimulates keratinocytes to produce endogenous proteases that exacerbate barrier dysfunction and produce proteases (staphopain and aureolysin) that inactivate AMPs.

Lipid Alterations and Skin pH

Skin lipids possess anti-inflammatory and antimicrobial properties. Free fatty acids and sphingoid bases, in particular, exhibit documented antimicrobial activity against *S. aureus*. Alterations in lipid composition – consistently observed in AD – represent a major cause of barrier dysfunction, particularly involving ceramides, cholesterol, and free fatty acids, with accumulation of short-chain ceramides, reduction of very-long-chain ceramides, and increased transepidermal water loss (TEWL) [14].

Skin bacteria release lipid vesicles containing potent pro-inflammatory molecules known as MAMPs (microbe-associated molecular patterns), recognized by keratinocytes and leukocytes in the granular layer and deeper tissues, eliciting an innate immune response[15]. Barrier defects may facilitate the penetration of these vesicles, leading to chronic skin inflammation.

Free fatty acids on the skin's surface create a low-pH environment (pH 4-6) that plays a key regulatory role in antimicrobial defense, barrier homeostasis, inflammation, and itch mediation – directly and indirectly through the pH–serine protease and protease-activated receptor 2 (PAR2) axis [16,17] – and support commensal microflora,

which acts as a first-line defense against pathogens via competition, immune modulation, and barrier support [18].

Low pH regulates ceramide synthesis through β-glucocerebrosidase and acid sphingomyelinase activation, the action of which is impaired at neutral pH. Acid sphingomyelinase also regulates cathepsin D, involved in epidermal differentiation. An acid pH also reduces expression of *S. aureus* adhesion proteins (clumping factor B and fibronectin-binding protein) that bind host cytokeratin 10 and fibronectin [10].

Th2 immunity and inflammation

AD is associated with Th2-driven inflammation. Skin scratching, environmental insults, and bacterial colonization promote the release of alarmins (IL-1α, IL-33, IL-18, IL-36), inducing epidermal hyperplasia and type 2 inflammation [19].

The action of IL-4 and IL-13 is particularly prominent, as they act by reducing the expression of FLG, human β-defensin genes HBD-2 and -3 and fatty acid elongases (ELOVL3, ELOVL6), leading to reduced ultra-long-chain fatty acids and impaired EOS-ceramide synthesis [20], ultimately compromising barrier integrity. These cytokines also enhance susceptibility to *S. aureus* toxins such as α-toxin, increasing keratinocyte cytotoxicity.

Antimicrobial peptides such as LL-37 defensin (cathelicidine) and dermcidin are also reduced in AD skin [19].

Skin Microbiota and Dysbiosis in Atopic Dermatitis

The host immune system, microbiota, and pathogens interact dynamically. While the immune system shapes microbial communities, the microbiota stimulates host immunity, limits harmful inflammation, and prevents pathogen colonization [21].

Healthy skin supports commensals through nutrient and ligand production and mounts antimicrobial defenses via AMPs, cytokines, immune cells, and neuroimmune interactions [22]. Conversely, commensals contribute to skin health by producing AMPs, antibiotics, enzymes, and metabolites that influence pH and barrier function [23]. Microbial products can be synthesized de novo or derived from host metabolism, reflecting a bidirectional host–microbiota relationship [24].

Healthy skin displays high microbial diversity, including *Dermacoccus*, *Corynebacterium*, and coagulase-negative staphylococci (CoNS) such as *S. epidermidis*, *S. hominis*, *S. warneri*, and *S. capitis*, which produce bacteriocins targeting *S. aureus*. In contrast, AD skin shows dysbiosis, reduced diversity, and overgrowth of *S. aureus* [25]. Interestingly, children with AD and their healthy primary caregivers appear to share similar microbes (such as specific *S. aureus* strains producing particular enterotoxins), suggesting interpersonal transmission of skin microbiota that are capable of causing or exacerbating disease activity. This phenomenon is not observed in healthy caregivers of healthy children [26].

Finally, microbial diversity in patients with active AD is reduced in both lesional and non-lesional skin, proportionally to disease severity [27]. Although no correlation has been identified between skin microbiota composition in the first two months of life and the risk of developing AD in the first two years of age, a prospective cohort study of 300 Danish children with at least one atopic parent demonstrated that lower microbial diversity at two months correlates with an increased risk of developing AD [28].

COMMENSAL SKIN MICROORGANISMS

Coagulase-Negative Staphylococci (CoNS) and Gram Positive Anaerobic Cocchi (GPAS)

The best-characterized and most frequently isolated CoNS from human skin is *S. epidermidis* (SE) [4], a key member of the healthy skin microbiota, summarized in Table I [29].

Some studies have reported opposite effects in SE – keratinocyte interactions depending on whether the skin is healthy or affected by AD [30]. In healthy skin, SE activates the aryl hydrocarbon receptor (AHR) in dendritic and dermal/epidermal immune cells, modulating tissue and immune homeostasis as well as the skin microbiome. It also induces AMP, FLG, and LOR production, promotes barrier repair and keratinocyte differentiation, and regulates intercellular adhesion, thereby preventing transepidermal water loss.

AHR is also involved in inflammatory responses: the AHR/NRF2 axis (which upregulates barrier function by promoting FLG and antioxidant production) counteracts the JAK-STAT inflammatory pathway (which downregulates barrier function and increases oxidative stress) that is typical of AD patients [31].

Metabolites produced by commensal microbes can suppress inflammatory cytokine production and Th2 differentiation in an AHR-dependent manner, through ligands such as indole-3-aldehyde (IAld) [32]. Conversely, dysbiosis in AD skin leads to reduced IAld expression and decreased AHR activation, resulting in increased skin permeability, impaired barrier integrity, and enhanced inflammation and SA colonization [33].

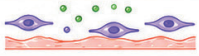
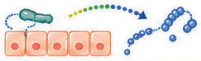
Therefore, AhR ligands, inducers, or modulators may represent novel therapeutic strategies in AD. Tapinarof emulsion, a specific AhR agonist, was already approved by the FDA in December 2024 for AD in children aged 2 years and older. Tapinarof emulsion is a highly effective, well tolerated, non-steroidal topical treatment option for patients down to 2 years of age with AD, which can be used without restrictions on duration of use, extent of body surface area treated, or sites of application, including on sensitive skin areas, including the face and neck [34].

S. hominis is the second CoNS most frequently isolated skin colonizer, particularly in moist and sebaceous areas such as the axillae, pubic region, and feet. Unlike SA and SE, *S. hominis* does not expand in AD lesional skin; thus, early-life colonization by *S. hominis* is associated with a lower risk of developing AD later in life [35].

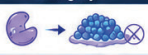
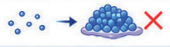
Table I. *Staphylococcus epidermidis* (SE) features in AD

Beneficial Functions and Bioactive Molecules of *Staphylococcus epidermidis* (SE) in Skin Homeostasis

A. Beneficial Functions of *Staphylococcus epidermidis* (SE)

Category		Key Function / Mechanism	Description	Contribution to Skin Homeostasis
	Inducing immune priming in neonates		Supports early immune system education and development.	Establishes a balanced immune response early in life.
	Maintaining an effective skin barrier *in vitro*		Contributes to epidermal integrity and barrier homeostasis.	Enhances barrier function and prevents transepidermal water loss.
	Mediating wound healing		Promotes tissue repair and regeneration processes.	Accelerates re-epithelialization and tissue recovery.
	Protecting against colonization by skin pathogens through cross-talk with keratinocytes		Enhances host defense mechanisms against pathogenic microorganisms.	Limits colonization and overgrowth of skin pathogens.
	Modulating the immune system (activation of CD8⁺ T cells and γδ T cells)		Activates CD8-positive T cells and γδ T cells, contributing to immune regulation.	Promotes immune surveillance and balanced immune responses.

B. Bioactive Molecules Produced by Genetically Diverse SE Strains

Category	Bioactive Molecule / Product		Description / Mechanism	Contribution to Skin Homeostasis
	Extracellular serine protease (Esp)		Inhibits *Staphylococcus aureus* (SA) biofilm formation.	Prevents SA biofilm establishment and persistence on the skin.
	Lantibiotics (epidermin and Pep-S)		Inhibit the growth of *Staphylococcus aureus* (SA).	Suppresses SA overgrowth and maintains microbial balance.
	Lipoteichoic acid		Suppresses inflammation and promotes wound healing via Toll-like receptor 2 (TLR2).	Reduces inflammation and supports epidermal repair.
	Bacteriocins (PSM γ and δ)		Enhance antimicrobial peptide (AMP) activity and limit pathogen survival on the skin surface.	Potentiates innate defense and limits survival of skin pathogens.
	Sphingomyelinase		Contributes to ceramide generation, prevents skin dehydration, and promotes SE colonization.	Strengthens barrier function and supports sustainable SE colonization.

AMPs, antimicrobial peptides; PSM, phenol-soluble modulins; SE, *Staphylococcus epidermidis*; SA, *Staphylococcus aureus*; TLR2, Toll-like receptor 2.

In a phase 1 randomized clinical trial, the antibiotic-producing *S. hominis* A9 strain (ShA9) showed promising results as a topical anti-SA treatment in AD patients [36]. Additionally, *S. hominis* can inhibit EcpA production by pathogenic SE strains.

Gram-positive anaerobic cocci (GPAC) of the genera *Finegoldia*, *Anaerococcus*, and *Peptoniphilus* are also typical skin commensals, although they are underrepresented in FLG-deficient skin.

Some GPAC produce enzymes (sortases) that promote strong adhesion to host tissues, enabling competition with SA in damaged skin. They may also act as danger signals, priming immune responses, inducing AMP release by keratinocytes and promoting skin repair in a partially AHR-dependent manner. Thus, GPAC may represent a target for prebiotic [37] or postbiotic therapies in AD [38].

Quorum Sensing and Microbial Communication

Quorum sensing (QS) is a bacterial communication mechanism that enables staphylococci to coordinate behavior based on population density through signaling molecules that allow individual cells to sense the overall bacterial load.

The purpose of QS is to optimize nutrient acquisition from the host under high-density conditions while eliminating competing bacteria with similar nutritional requirements [39].

By modulating gene expression, QS regulates toxin production, enzyme secretion, and virulence factors, promotes tissue colonization, and facilitates the formation of protective biofilms against antibiotics and immune cells.

Biofilm formation contributes to occlusion of eccrine sweat ducts, leading to inflammation and itching. It also enhances bacterial adhesion, promotes immune evasion, and protects against competing microbial species.

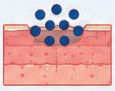
The QS gene cluster in SA is known as the accessory gene regulator (agr). At high population density, suprathreshold levels of autoinducing peptide (AIP) activate the transmembrane receptor AgrC, which, via the response regulator AgrA, induces toxin and protease production, contributing to inflammation and skin damage in AD [40].

Several SE strains produce AIPs that inhibit SA QS, favoring commensal dominance through microbial competition. However, in some cases, QS from other SE strains may further promote SA-induced inflammation. Since different strains possess unique AIP and AgrC variants, the interaction between SA and SE QS systems is highly strain-dependent [41].

For example, studies have shown functional heterogeneity among SE strains, with Agr type II variants more prevalent in AD patients and Agr type IV variants more common in healthy skin [42].

These findings suggest that QS-modulating therapies targeting SA

Table II. Key factors promoting *Staphylococcus aureus* (SA) colonization and persistence in atopic dermatitis (AD).

Stage / Process	Key Factor	Mechanism / Impact on SA Colonization in AD
 Predisposing factors	Increased expression of SA receptors	Upregulation of host receptors on keratinocytes facilitates SA attachment.
	Decreased AMPs such as cathelicidin (LL-37), β-defensins, and dermcidin [36]	Reduced antimicrobial activity diminishes innate defense, allowing SA overgrowth.
	Reduced presence of anti-SA commensal microbes	Loss of protective commensals decreases colonization resistance, favoring SA expansion.
	Increased expression of microbial surface components recognizing adhesive matrix molecules	Enhances SA adhesion to host extracellular matrix proteins (fibrinogen, fibronectin, and collagen) via MSCRAMMs.
	Reduced NMF levels in corneocytes	Low natural moisturizing factors increase exposure of corneodesmosin (CDSN), which interacts with bacterial adhesins to promote SA adherence.
	Presence of Th2 cytokines (IL-4, IL-13)	Th2 cytokines inhibit structural proteins (filaggrin, loricrin, and involucrin), weakening barrier integrity and increasing SA colonization.
 SA biofilm formation and virulence	Biofilm formation and toxin production	Following adhesion, SA forms biofilms, produces toxins that inhibit competing staphylococcal strains [46], and releases pro-inflammatory virulence factors contributing to barrier damage.
	Increased toxin production in lesional skin	Toxin production is increased in AD lesional skin and correlates with disease activity [36].
	Ceramidase secretion	SA-secreted ceramidase reduces levels of ceramides, triglycerides, and unsaturated free fatty acids, increasing skin permeability to allergens and raising skin pH, further promoting SA growth [47].
 Host metabolic factors	Inhibition of adipogenesis	Inhibition of adipogenesis also reduces LL-37 production by dermal adipocytes, further increasing susceptibility to SA colonization [48].
 Impaired innate immune responses	Inhibition of neutrophil effector functions	SA can inhibit neutrophil effector functions—including extravasation, priming, activation, phagocytosis, and neutrophil extracellular trap formation—thereby impairing early control of skin colonization [49].

SA, *Staphylococcus aureus*; AD, atopic dermatitis; AMPs, antimicrobial peptides; NMF, natural moisturizing factors; CDSN, corneodesmosin; Th2, T helper 2; IL, interleukin; MSCRAMMs, microbial surface components recognizing adhesive matrix molecules.

and SE may reduce virulence. Additionally, topical application of probiotic SE strains with "beneficial" QS profiles may counteract SA pathogenic effects via interspecies modulation of the skin microbiome [41].

Factors influencing SA colonization in AD skin

Skin colonization by SA occurs in 30-100% of AD patients [43], compared to approximately 20% of healthy individuals. Colonization often precedes and may predict AD development in childhood [35], affecting both lesional and non-lesional skin [43].

SA-colonized AD patients represent a distinct phenotype characterized by increased disease severity, pronounced Th2 skewing, greater barrier dysfunction, and enhanced allergic sensitization compared to non-colonized patients [44], thereby promoting the atopic march and food allergy development [45].

Dysbiosis activates inflammatory pathways that exacerbate barrier damage, creating a vicious cycle between inflammation and microbial imbalance. Key factors promoting SA colonization in AD [36, 46-49] are summarized in Table II.

CONCLUSIONS

The growing understanding of host-skin microbiota interactions has generated considerable interest in delving deeper into the complex pathogenic mechanisms of AD and developing targeted therapeutic approaches. However, clinical data on this topic are still limited, and evidence of the centrality of host-skin microbiota interactions is only theoretical. Therefore, more innovative studies that establish the efficacy and safety of therapeutic strategies for managing AD are currently being explored, the results of which will be needed to implement a truly comprehensive approach to AD, possibly focusing on identifying reproducible microbial profiles, clarifying the specific effects of individual microbial strains, and developing adjuvant targeted intervention strategies in AD.

Glossary

Microbiota: the ensemble of microorganisms colonizing the host Microbiome: the genetic information contained within the microbiota that colonizes the host. Holobiont: the host together with its microbiota. Holobiome: the genome resulting from the combined genomes of the host organism and its colonizing microorganisms.

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Ethical consideration
Since this study analyzed previously published primary data, ethical approval was not required.

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Conflict of interest statement
The authors declare that they have no competing interests.

Authors' contributions
NM conceived the manuscript. FC, BG, PC,GM, EG wrote the first draft and finalized it. All authors revised the manuscript and approved the final version.

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