



CME Review

On the surface

Skin microbial exposure contributes to allergic disease

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Key Messages

- The commensal-epidermal homeostasis within healthy skin protects against allergic disease by inducing epidermal accumulation of commensal-specific type 1 and type 17 immune cells and increasing the expression of antimicrobial peptides and alarmins that target proallergic bacteria.
- The composition of skin microbiome and epidermal barrier integrity are interdependent, and disruption in one (eg, filaggrin mutations or dysbiosis) disrupts the other.
- Skin microbiome dysbiosis contributes to progression and exacerbation of allergic diseases, such as atopic dermatitis, food allergy, allergic rhinitis, and asthma.
- Current and potential treatments affecting the skin microbiome include emollients, restoration of skin commensals and antimicrobial peptides, and anti-T_H2 biologic therapy.
- Maintenance of the skin barrier is the primary prevention for the development or exacerbation of atopic disorders; however, studying preventions targeting the skin microbiome is needed.

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ABSTRACT

Objective: To discuss the skin microbiome modulates immunity by interactions between skin immunology with keratinocytes to combat pathogens. Allergic disorders are classified by immunoglobulin E sensitivity and aberrant T_H2 cell responses, and an increasing number of studies have described the associations with skin microbiome fluctuations. In this review, we discuss commensal-epidermal homeostasis and its influence on allergic disease.

Data Sources: All included references were obtained from the PubMed database.

Study Selections: Studies addressing relevant aspects of commensal-epidermal homeostasis, skin microbiome dysbiosis, microbiome-targeted therapeutics, and prevention in allergy were included.

Results: Homeostasis between the commensal microbiome and the epidermis is important in protecting against allergic disease. Commensals promote antiallergic T_H1 and T_H17 immunophenotypes within the skin and induce keratinocytes to secrete antimicrobial peptides and alarmins that enhance barrier function and antagonize proallergic organisms. Perturbations in this homeostasis, however, is associated with allergic disease development. Atopic dermatitis is associated with decreases in skin commensals and increases in the

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pathogen, *Staphylococcus aureus*. Fluctuations in the skin microbiome contributes to decreased barrier dysfunction, allergic sensitization, and T_H2 cytokine secretion. Little is known about how the skin microbiome affects food allergy, allergic rhinitis, and asthma, and it is poorly understood how cutaneous inflammation influences systemic allergic responses. Therapies are targeted toward maintenance of the skin barrier, replacement of healthy commensals, and anti-T_H2 biologic therapy.

Conclusion: Although the effects of commensal-epidermal homeostasis on allergy within the skin are becoming increasingly clear, future studies are necessary to assess its effects on extracutaneous allergic disorders and explore potential therapeutics targeting the skin microbiome.

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Introduction

Allergic disorders, characterized by immunoglobulin (Ig)E sensitivity, are steadily rising in prevalence worldwide and markedly affect the quality of life in all age groups.¹ A growing body of literature is revealing that the skin microbiome, the community of bacteria, viruses, and fungi present on the skin, plays a substantial role in modulating allergic disorders. The microbiome is vital for the development of the immune system and homeostasis. Changes in microbial composition and function, termed dysbiosis, have been linked to alterations in immune responses and to the development of allergic diseases. Here, we provide a comprehensive review on the impact of the skin microbiome on allergic disease, including atopic dermatitis (AD), allergic asthma, food allergy, and allergic rhinitis (AR). We discuss the modulation of allergic disease by commensal-epidermal homeostatic interactions and the role of the skin microbiome in major allergic diseases. Finally, we discuss the implications of the skin microbiome on allergic disease diagnosis, therapeutics, and prevention.

Mechanisms of Commensal-Epidermal Homeostasis

The human skin microbiome is a highly variable community of bacteria, viruses, and fungi (Table 1) on the skin that modulates host immunity and provides protection from pathogens. The composition of the microbiome is site specific, varying with the physiological environments at each body site.² Body sites differ by pH, fatty acid (FA) composition, and ability of the skin to retain water but can be influenced by sex, antibiotic treatment, and cosmetic use.³ These factors in turn affect microbial ecology.³ Site-specific microbial communities (Table 1) develop around 3 months of age,⁴ and early-life colonization is needed for the development of commensal tolerance and decreased risk of allergic diseases, such as asthma.⁵ In the skin, microbial ecology also varies by depth within the epidermis.⁶ There is a growing body of literature regarding the human skin microbiome composition under healthy and pathogenic states and the homeostatic interactions between normal skin commensals and the epidermis. As discussed subsequently, healthy commensal-epidermal homeostasis predominantly protects against allergic disease by promoting barrier function, deterring colonization of proallergic pathogens, including *Staphylococcus aureus*, and maintaining an antiallergic T_H1 and T_H17 immunophenotype.

Commensal-Epidermal Homeostasis: Epidermal Barrier-Mediated Immunity

The skin consists of the dermis and epidermis (Fig 1), with the latter subdivided into stratum basale, stratum spinosum, stratum granulosum (SG),⁷ and stratum corneum (SC). Barrier integrity is primarily maintained by the SC layer and tight junctions (TJs) within the SG. The SC is composed of a cornified envelope, in which keratinocytes containing crosslinked structural proteins, such as filaggrin (FLG), are connected by corneodesmosomes, and a lipid-rich lamellar layer is produced and secreted by keratinocytes.^{8,9} Tight junctions are multimeric protein complexes that physically

link keratinocytes within the SG.¹⁰ Together, the SC and TJs form a physical barrier impermeable to microbes, including skin commensals.⁹ However, as discussed subsequently, disruptions in epidermal-microbiome homeostasis can compromise SC or TJ formation and function, thereby disrupting the skin barrier and increasing susceptibility to allergic disease.^{8,11,12}

Filaggrin

Mutations in *FLG* or disrupted *FLG* expression or processing alters epidermal-microbiome homeostasis which can predispose to microbial invasion,¹³ altered microbiome composition (ie, reduced diversity),^{14,15} increased susceptibility to viral and bacterial skin infections,¹⁶ and increased risk of allergic sensitization.¹⁷ Reduced *FLG* levels and reduced *FLG* processing are major risk factors for allergic sensitization and allergic disease,¹¹ and vice versa. *FLG* expression is reduced by proallergic T_H2 cytokines.^{1,13,18} Reduced *FLG* expression and commensal dysbiosis may thus create a positive feedback loop culminating in a dysfunctional barrier and predisposition to allergic disease.

Epidermal proteases and antiproteases

Keratinocyte desquamation is regulated by the balance between kallikrein proteases (KLKs) that cleave *FLG* and corneodesmosomes, and antiproteases, namely lymphoepithelial Kazal-type–related inhibitor, encoded by *SPINK5*.¹⁹ Reduced corneodesmosomes, reduced lymphoepithelial Kazal-type–related inhibitor, or unchecked KLK activity is associated with AD and other atopic diseases.^{20–22} Indeed, individuals with Netherton syndrome (NS), caused by *SPINK5* mutations, often exhibit AD, elevated IgE, and varying degrees of asthma, food allergy, and AR.^{20,21} Individuals with NS are also susceptible to recurrent skin infections and dysbiosis, including infection by *S aureus*, which can further disrupt barrier function.²³ Finally, *S aureus* phenol-soluble modulins enhance epidermal KLK activity and promote barrier dysfunction.²⁴

SC lipids

The lipids of the lamellar layer include cholesterol, FAs, and ceramides^{8,25} that may influence skin microbiome composition, skin barrier function, and allergic disease susceptibility. The FAs contribute to the acidic epidermal pH that favors commensals over proallergic bacteria.²⁶ The skin, abundant in ceramides and long-chain FAs, is associated with an increased abundance of normal skin commensals, such as *Corynebacterium* and *Cutibacterium*.¹⁴ In addition, long-chain FAs exert antimicrobial activity against bacteria, fungi, and enveloped viruses.²⁷ Perturbations in the lipidome, however, can induce epidermal barrier defects and are associated with AD.^{8,25,26} For example, reduced ceramides, long-chain FAs, and expression of FA elongases (which synthesize long-chain FAs) have been observed in the epidermis of individuals with AD,²⁸ and T_H2 cytokines can suppress FA elongase expression in human keratinocytes.²⁸

Tight junctions

The importance of TJs as an epidermal barrier component is highlighted by its frequent targeting for destruction by allergens and proallergic pathogens.^{29,30} *S aureus*, for example, prevents TJ

Table 1
Commensal Skin Organisms and Skin Pathogens in Allergic Disease

Common commensal organisms of the healthy skin microbiome				
Microbiome component	Phyla	Genera	Species	Source
Bacterial skin microbiome	Actinobacteria	Corynebacteria	C acnes	4,32,101,102
		Cutibacteria ^a	S epidermidis	
	Firmicutes	Staphylococci	S epidermidis	
	Proteobacteria	Roseomonas	R mucosa	
Skin mycobiome	Basidiomycota	Malassezia	M furfur, M restricta, M globosa, M sympodialis	55
	Ascomycota	Candida	C albicans	
		Viral taxa		
Skin virome	Phages	Pseudomonas phage, Bacillus phage, Staphylococcus phage, Propionibacterium phage, Planktothrix phage, Streptococcus phage, Burkholderia phage, Mycobacterium phage		58,59
	Other	Human papillomavirus		
Pathogenic organisms of the skin microbiome in allergic disease				
Microbiome component	Phyla	Genera	Species	Source
Bacterial skin microbiome	Actinobacteria	Corynebacteria	C striatum	64,69,109
	Firmicutes	Staphylococci	S aureus	
		Streptococci	S pyogenes	
Skin mycobiome	Basidiomycota	Malassezia	M dermatis, M sloofiae, M sympodialis	71,72
	Ascomycota	Candida	C albicans	
		Viral taxa		
Skin virome	Herpesviridae	HSV		109
	Poxviridae	Molluscum contagiosum, Vaccinia virus		

Abbreviation: HSV, herpes simplex virus.

^aFormerly, *Propionobacteria*.

complex membrane localization, thereby reducing intercellular connectivity and increasing epidermal permeability.¹² TJ perturbations can further disrupt the SC by reducing FLG and lamellar lipid synthesis and are associated with AD.³¹ In contrast, commensal *S. epidermidis* promotes TJ formation both directly and indirectly by inducing keratinocyte antimicrobial peptide (AMP) secretion (discussed subsequently).²⁹

Skin pH

The acidic pH range of 4 to 6 of the healthy epidermis favors commensal over proallergic bacteria.^{26,32} Contributors to this acidic pH are natural moisturizing factors (which are byproducts of FLG catabolism) and FAs produced by keratinocytes or as metabolites of

commensal bacteria (eg, *Cutibacterium acnes*).^{26,32} This acidity antagonizes pathogens by several means, including reducing *S. aureus* keratinocyte adhesion and altering the conformation and activity of *S. aureus* virulence factors.²⁶ However, the inability to maintain acidic skin (eg, defective FLG catabolism) alters microbial diversity and allows *S. aureus* keratinocyte adhesion,^{26,32} indicating the importance of skin pH in commensal-epidermal homeostasis.

Commensal-Epidermal Homeostasis: Keratinocyte-Mediated Immunity

Keratinocytes release a multitude of proteins that can affect commensal-epidermal homeostasis and thus influence allergic

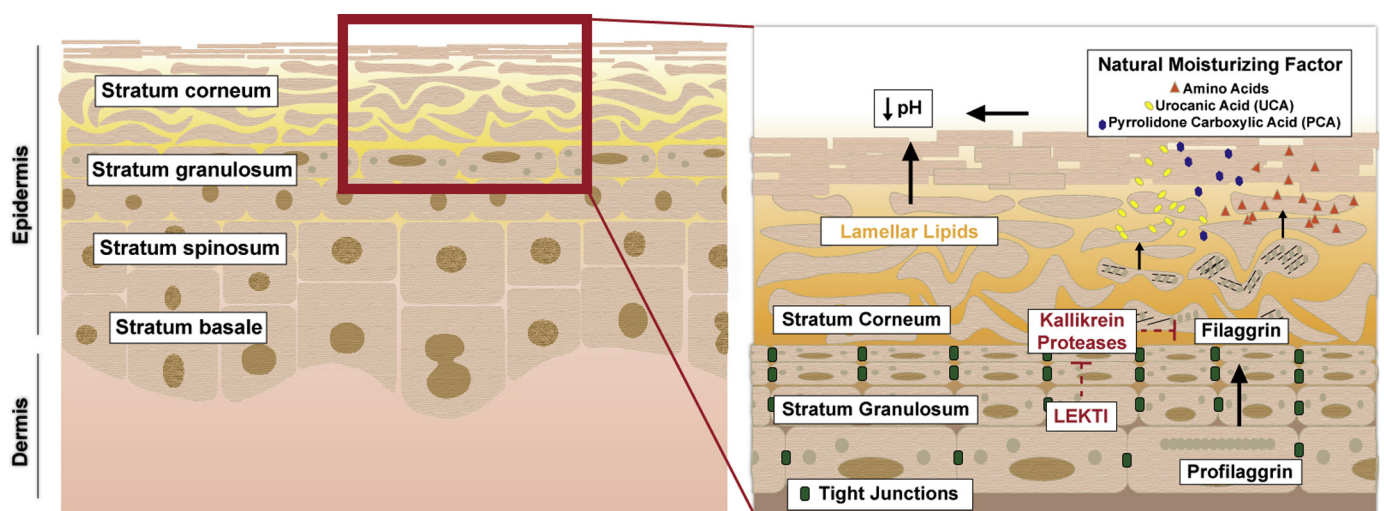
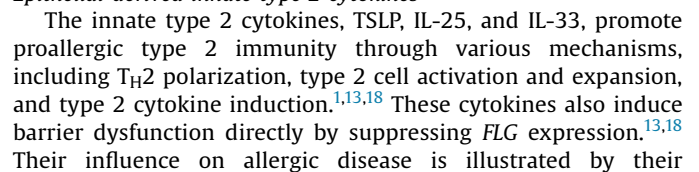


Figure 1. Properties of the epidermal barrier. The skin consists of dermis and epidermis, which is further subdivided into stratum basale, stratum spinosum, SG, and SC. The epidermal barrier is formed primarily by (A) TJs within the SG and (B) the SC. The SC consists of lamellar lipids (eg, ceramides and long-chain fatty acids) and a cornified envelope. NMFs (byproducts of FLG catabolism) and FAs of the lamellar layer create an acidic pH. KLKs promote desquamation by degrading FLG and corneodesmosomes. The KLKs are inhibited by LEKTI. FA, fatty acid; FLG, filaggrin; KLK, kallikrein protease; LEKTI, lymphoepithelial Kazal-type–related inhibitor; NMF, natural moisturizing factor; PCA, pyrrolidone carboxylic acid; SC, stratum corneum; SG, stratum granulosum; TJ, tight junction; UCA, urocanic acid.



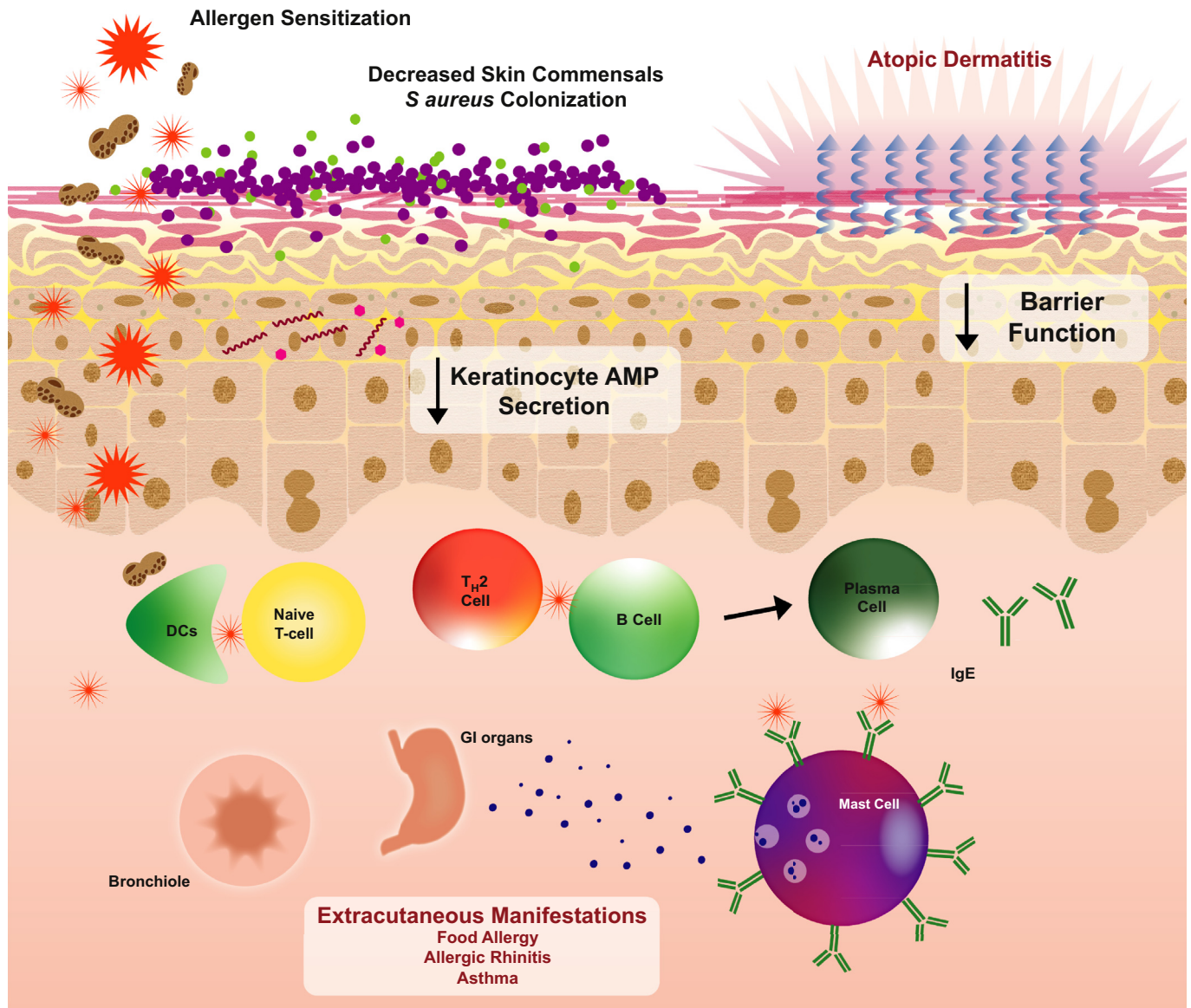


Figure 3. Effect of the skin microbiome on allergic disease. A decrease in skin commensals and the presence of pathogens contribute to skin microbiome dysbiosis that can occur in allergic disease. Decreases in keratinocyte AMPs also prevent clearance of these pathogens. In particular, *Staphylococcus aureus* is found to decrease barrier function, induce IgE production, and induce secretion of T_H2 cytokines, which can have systemic consequences and exacerbate extracutaneous manifestations of allergy. AMP, anti-microbial peptide; DC, dendritic cell; GI, gastrointestinal; IgE, immunoglobulin E; T_H , T-helper.

association with an AD-like phenotype if increased within the skin^{13,18,44} and, for TSLP specifically, an asthma-like phenotype if it enters the systemic circulation.^{45,46} Various proallergic stimuli induce TSLP, IL-25, and IL-33 production, including type 2 cytokines, allergens, and mechanical damage.^{1,13,18} The skin microbiome also can influence their synthesis; for example, notch-deficient mice exhibit skin inflammation and systemic atopy and have higher epidermal TSLP mRNA and serum TSLP levels in the absence vs presence of normal commensals.⁴⁷ Proallergic *S aureus*, in contrast, induces TSLP and IL-33 expression by keratinocytes.^{48,49}

Commensal-Epidermal Homeostasis: Adaptive Immunity

Bacterial microbiome

Just as in the gut, recent studies have revealed that commensal bacteria protect against allergic disease by priming the adaptive

immune system. In addition to directly inducing AMPs from keratinocytes, commensal *S epidermidis* in mice primes epidermal accumulation of commensal-specific T_H1 and T_H17 and cytotoxic T cell 1 (Tc1) and Tc17.^{42,50,51} Commensals induce these cells to secrete IL-17A which promotes keratinocytes to produce anti-allergic peptides, such as s100a8 and s100a9.⁴² Similarly, commensal *Corynebacteria accolens* can induce epidermal IL-17A+ $\gamma\delta$ -T cell influx, thereby promoting a type 17 immunophenotype.⁵² Commensal-specific Tc17 T cells can promote barrier integrity in mice directly by expressing tissue-repair genes and accelerating wound healing.⁵⁰ Interestingly, *S epidermidis* can suppress *S aureus* colonization when the skin barrier is intact, but when disrupted (eg, tape-stripping) it instead promotes *S aureus* colonization.⁵³ This phenomenon may be explained by a poised T_H2 transcriptional profile identified within *S epidermidis*-specific Tc17 and T_H17 cells which, on exposure to proallergic innate type 2 cytokines, is translated, thereby superimposing or substituting the type 17 profile.⁵⁴

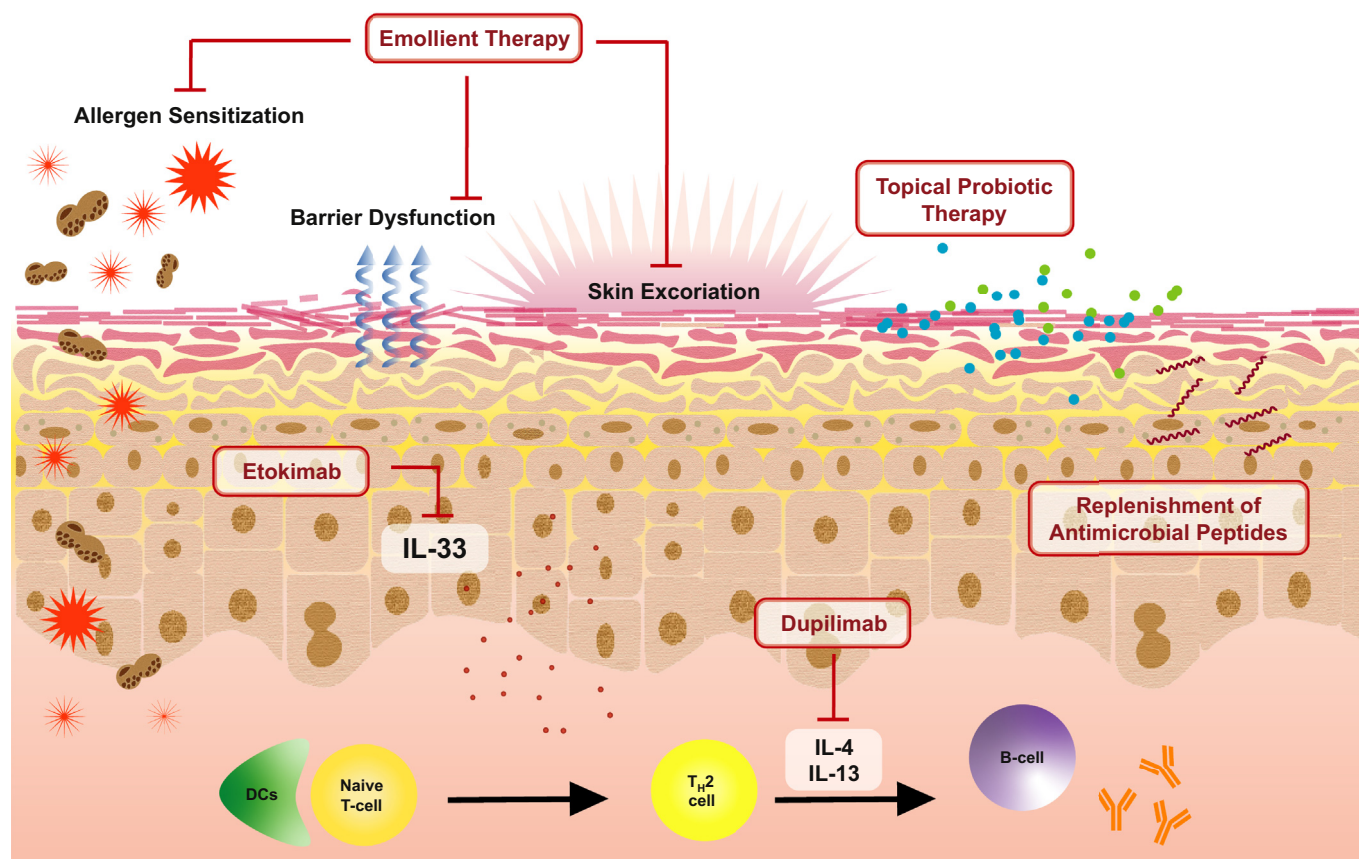


Figure 4. Interventions influencing the skin microbiome. Emollient therapy aids in repairing a damaged skin barrier preventing inflammation and sensitization. The replacement of skin commensals and AMPs is also being studied as potential therapeutics. Biologic therapeutics, which act by blocking cytokines implicated in allergic disease, such as IL-33, IL-4, and IL-13, may also have an impact on skin microbiome dysbiosis. AMP, antimicrobial peptide; DC, dendritic cell; IL, interleukin; T_H, T-helper.

Mycobiome

Information regarding the mycobiome's influence on allergic disease development is limited, and available studies draw contradicting conclusions. For example, many *Malassezia* species induce *Malassezia*-specific T_H17 cells⁵⁵ and keratinocyte hBD production,⁵⁶ which protects from allergy (see subsequent discussion). In contrast, *Malassezia globosa* and *restricta* can promote proallergic TSLP release from keratinocytes,⁵⁶ and *Malassezia*-specific IgE and T_H2-polarized T cells have been reported in patients with AD.⁵⁷ Further study is warranted to determine how fungal commensals influence allergic disease and if these effects are species-dependent, context-dependent, or both.

Virome

The typical skin virome is not well characterized, nor is its role in allergic disease. In an analysis of double-stranded DNA viruses, bacteriophages were prevalent on human skin⁵⁸ (Table 1) and topical phage therapy reduced AD severity in 1 study, though the mechanism is unclear.⁵⁹ More controlled and mechanistic studies are nevertheless required to address the role of the skin virome in allergic disease.

The Skin Biome in Allergic Disease

Atopic Dermatitis

AD affects 10% to 20% of children worldwide, often in industrialized countries,⁶⁰ with onset before 1 year of age in up to 60% of children.⁶¹ Healthy and AD skin exhibit many structural and immunologic differences. AD is also characterized by skin microbiome dysbiosis. However, whether these microbiome disruptions

precede^{62,63} or cause^{14,15} skin disease or are a consequence of disease remains unclear. Studies suggest that commensals may play a role in preventing AD because commensal staphylococcal colonization at 2 months of age is associated with decreased AD incidence at 1 year⁶² and commensals are positively correlated with the levels of long-chain FAs.¹⁴ The loss of commensal abundance is correlated with individuals that have FLG deficiency.¹⁴ Decreased commensal abundance is also observed during AD flares but can be reversed with bleach baths, emollients, or topical steroids.⁶⁴ Birth cohorts suggest that infants who develop AD have a decrease in the heterogeneous commensal population,⁶⁵ which is accompanied by increased abundance of the pathogen *S aureus*. Infants with *S aureus* colonization or who lack *S aureus*-inhibiting commensals³⁹ at 3 months are more likely to develop AD compared with those who are not colonized.⁶³

Various *S aureus* virulence factors have been associated with AD.^{66,67} The *S aureus* cell wall component lipoteichoic acid upregulates over 300 genes in keratinocytes, including T_H2-polarizing genes, such as TSLP and IL-4. In addition, lipoteichoic acid reduces FLG expression.⁶⁸ *S aureus* also secretes enterotoxins capable of inducing inflammation by acting as superantigens and activating the T cells by major histocompatibility complex II. Individuals with AD have more specific IgE to the *S aureus* alpha, delta, and toxic shock syndrome toxin-1 toxins than healthy controls. *S aureus*-derived phenol-soluble modulins can also increase keratinocyte KLK activity,²⁴ which may promote *S aureus* skin penetration by increasing desquamation and reducing barrier integrity (Fig 3).

Corynebacterium species are another common skin commensal (Table 1). Although *C accolens* may protect from allergy by

promoting IL-17A+ $\gamma\delta$ -T cell aggregation,⁵² *Corynebacterium* may be involved in allergic disease by the induction of type 2 responses.⁵ *C striatum* can increase expression of genes associated with *S aureus* carriage in the nares, suggesting that *C striatum* promotes a shift toward *S aureus* commensalism.⁶⁹ Several studies have revealed the presence of *Corynebacterium* in individuals with AD.⁷⁰

Malassezia species are common fungi on skin (Table 1), and healthy individuals have *Malassezia*-specific T cells and antibodies.⁵⁵ However, subjects with AD are characterized by the presence of *M dermatis* and *M sloofiae*,⁷¹ and several studies reveal the presence of *Malassezia*-specific IgE⁵⁷ in individuals with AD. Moreover, the presence of *Malassezia*-specific IgE has been correlated with increasing severity of AD in adults. *Malassezia* antigens can induce autoreactive T cells, which induce further inflammation independent of the fungal antigens.⁷² *Malassezia* exposure led to SC colonization, myelocytic infiltration, and IL-17 induction in mice.⁵⁵ This IL-17 induction was crucial for controlling fungal burden; however, presence of *Malassezia* on the disrupted skin barrier induced inflammation, and IL-17-deficient mice had a diminished inflammatory response in *Malassezia* overgrowth.⁵⁵ These studies reveal that *Malassezia*-driven inflammation promotes AD-like disease in mice.⁵⁵ Studies are needed to characterize the differences, transition, or expansion of *Malassezia*-specific memory T cells in healthy adults vs those with AD.

The skin microbiome also extends protection against viral pathogens.⁷³ Children with AD are susceptible to viral infections, though these are less common than bacterial infections. Viral infections are known as complications of AD rather than a direct contributor to its pathogenesis. The most common viral infection in children with AD is herpes simplex virus, which causes eczematous herpeticum (EH). The EH manifestations range from fever and malaise to encephalitis or septic shock and are recurrent in up to 25% of the cases.⁷⁴ Viral infections are more likely in those with severe AD and often occur concurrently with *S aureus* infections.⁷⁴ In fact, *S aureus* alpha-toxin aids in herpes simplex virus infection by promoting viral binding to keratinocyte receptors.⁷⁵ T-cell lines generated from individuals with EH revealed increased secretion of IL-4⁺ when compared with T-cell lines generated from healthy controls, suggesting that virus-specific T cells generate a type 2 response in EH.⁷⁶ Treatment of AD with topical corticosteroids did not prevent subsequent EH, nor did interferon gamma therapy result in symptom improvement.⁷⁴

Molluscum contagiosum is a common childhood viral infection caused by a DNA virus of the poxviridae family. Although molluscum is usually self-limiting, those with AD experience prolonged infection with a more widespread distribution. Skin barrier defects, such as *FLG* mutations, can predispose to molluscum infection, whereas AD-induced pruritus promotes autoinoculation.^{77,78}

Patients with AD who had previously received a smallpox vaccination can develop eczema vaccinatum, characterized by disseminated vaccinia virus, which, if systemic, is lethal.⁷⁹ *FLG* seems to protect from vaccinia, as *FLG*-deficient mice had disseminated vaccinia infection.⁸⁰ As such, alternatives to the current smallpox vaccine are needed in those with AD. Imvamune, a vaccine using the modified vaccinia ankara virus, is safe in patients with mild-moderate AD and elicits a specific immune response.⁸¹

Food Allergy

Food allergy affects approximately 1 in 13 children in the United States and is defined as type 1 hypersensitivity to a given food antigen.⁸² The LEAP and LEAP-ON studies (n = 640) observed that skin and nasal *S aureus* colonization in children is associated with concurrent eczema. Total and specific IgE, particularly to egg white and peanut, were associated to *S aureus* colonization of the skin but

not the nares, suggesting that IgE sensitization may be promoted by skin biome interactions. However, this study is limited by use of less sensitive culture techniques to collect *S aureus*; thus, future studies should test these associations with sequencing-based approaches.⁸³ Further studies of the effect of the skin microbiome on food allergy are needed.

Allergic Rhinitis

AR is characterized by seasonal allergens that trigger upper airway inflammation inducing rhinorrhea, sneezing, and nasal congestion. AR affects up to 25% of the global population and steadily continues to rise.⁸⁴ The nasal cavity harbors its own community of organisms to defend against environmental insults.⁸⁵ A study sampling *S aureus* from both children and adults revealed that 85% of the subjects were colonized with *S aureus* in the nares and approximately 77% of the subjects with AD colonized by *S aureus* in the nares were also colonized on the skin.⁸⁶ These findings suggest that *S aureus* proliferates in the nasal cavity and a connection exists between the biomes at these 2 surfaces.

Asthma

Allergic asthma affects up to 18% of the global population and is defined by airway hyperresponsiveness and airway inflammation.⁸⁷ A major risk factor for asthma development is allergic sensitization.⁶⁰ The absence of skin commensals and antimicrobial responses⁴² predisposes to microbiome dysbiosis, associated with inflammation and T_H2 responses.

Organisms in household dust can be transferred to the skin through surfaces,⁸⁸ and those sharing a household have been reported to have similar skin commensals,⁸⁹ highlighting the influence of the environment on the skin microbiome. *S aureus* persists in dust⁹⁰ and is highly abundant in the microbiome of purified house dust mite bodies.⁹¹ Interestingly, *Staphylococcus*, *Hemophilus*, and *Corynebacterium* species in house dust are associated with increased asthma risk, whereas house dust levels of cockroach, cat, and mouse allergens are inversely related to asthma development in an early-life cohort.⁹² IgE sensitization to house dust mite⁹³ and *S aureus* is common in those with asthma and AD,⁹¹ and percutaneous exposure to *S aureus* by house dust mite exposure could be another potential route for sensitization to *S aureus*. Bacterial antigens in house dust that encounter the skin may reduce barrier integrity. The possibility that bacterial antigens are taken up through the skin in addition to the airways may provide insight into the progression of atopic comorbidities.

Therapeutic Interventions

Understanding the role of the skin microbiome in allergic disease and the underlying mechanisms has revealed unique opportunities for targeted therapy (Fig 4).

Emollients

Although their utility in AD prevention has recently been cast into doubt,⁹⁴ emollients are typically first-line therapy for AD, reducing the need for pharmaceutical interventions⁹⁵ and decreasing AD severity.⁹⁶ Emollient administration increases bacterial diversity⁹⁶ and decreases *S aureus* detection in lesional skin.⁹⁷ Coal tar emollients are an established AD therapy as they activate the aryl hydrocarbon receptor and, thus, induce keratinocyte differentiation, increase *FLG* expression, reduce T_H2 responses, and decrease the abundance of proallergic *S aureus*.⁹⁸

Emollients are also an efficient vehicle for other potential therapies, including those that specifically target the skin microbiome. Commensal- and keratinocyte-derived AMPs (eg, hBDs and LL-37) prevent or reduce pathogen colonization.^{39,40} Therefore,

emollients combined with AMPs may be an effective treatment for allergic diseases. In fact, the application of emollients containing bacteria-derived *Sh*-lantibiotics to individuals with AD reduced detectable *S aureus*.³⁹ Emollients containing keratinocyte AMPs may also be useful to treat biofilms because LL-37 was able to eradicate preexisting biofilms of methicillin-resistant *S aureus* in a wounded skin model without compromising keratinocyte function.⁹⁹ However, additional in vivo studies are needed to establish the utility and effectiveness of replenishing AMPs through emollients or other means.

Probiotics

An alternative to utilizing AMPs is the transplantation of microbes themselves. Living microorganisms that modulate the existing microbiota are known as probiotics.¹⁰⁰ The commensal *Roseomonas mucosa* isolated from healthy individuals inhibited *S aureus* growth in vitro, and its application to the skin of an AD mouse model decreased *S aureus* colonization and improved barrier function.¹⁰¹ Furthermore, the use of topical *R mucosa* in individuals with AD revealed that the probiotic use was associated with decreased disease severity and *S aureus* burden with no adverse events or treatment complications.¹⁰² Oral probiotics have modest effects in those with moderate to severe AD, but little effect in those with mild disease.¹⁰³ It will be interesting for future studies to assess whether *S epidermidis* or other commensals would be effective in oral or topical probiotics and to determine the contribution of individual species or strains to improved AD outcomes.

Biologics

The type 2 cytokines, IL-4 and IL-13, affect the skin microbiome by suppressing keratinocyte-derived AMPs and thus weakening microbial defenses. IL-4 and IL-13 also increase the efficacy of *S aureus* alpha-toxin, ultimately perpetuating cell death.¹⁰⁴ The human monoclonal antibody dupilumab blocks the IL-4 and IL-13 receptors and, thus, reduces their effector functions. The AD-LIBERTY EXPLORE study subjected patients with moderate to severe AD to either weekly treatments of dupilumab or a control and found that subjects treated with dupilumab had increased microbial diversity and decreased *S aureus* in both nonlesional and lesional skin.¹⁰⁵ Additional studies are necessary to elucidate the underlying mechanisms and determine the impact on other organisms.

As discussed previously, the innate type 2 cytokine IL-33 is associated with both local and systemic allergic responses when released from epidermal keratinocytes in response to damage, allergens, or *S aureus* colonization.^{1,13,18} The downstream effects of IL-33 include increased IgE and decreased *FLG* expression. Etokimab is a humanized monoclonal antibody against IL-33; its efficacy was assessed in 12 adult patients with moderate to severe AD. Etokimab reduced AD severity by over 50% with only minimal adverse effects.¹⁰⁶ Although the trial did not directly evaluate the effect of etokimab on *S aureus* colonization, anti-IL-33 therapy may be useful to abrogate dysbiosis-induced inflammatory responses.

Can the Skin Biome Aid Diagnosis and Prevention

AD is a clinical diagnosis lacking biomarkers or diagnostic testing. Skin dysbiosis often occurs before the presentation of AD symptoms making the microbiome a potential diagnostic tool. Unfortunately, although the influence of pathogens on atopy has been found,^{63,65,67,107–109} there are obstacles preventing the efficient, cost-effective, and reliable use of the microbiome for diagnostic purposes.¹¹⁰ Currently, metagenomic analysis is expensive, nonquantitative, and difficult to interpret in a clinical laboratory setting, making it a poor diagnostic tool.¹¹¹ In addition, despite the fact that *S aureus* colonization has been associated with

increased AD severity in many studies,^{7,112} *S aureus* colonization status does not influence current clinical practice.⁶¹

Primary prevention of AD is focused on maintenance of the skin barrier. The Barrier Enhancement for Eczema Prevention trial and the Prevention of Eczema By a Barrier Lipid Equilibrium Strategy trial are randomized control trials in which infants are subjected to standard skin care regimens or standard skin care in addition to a designated emollient.^{113,114} The Prevention of Eczema By a Barrier Lipid Equilibrium Strategy trial is distinguished by the use of an emollient based on the ratio of ceramides, cholesterol, and FAs.¹¹⁴ Although no statistically significant effect was found, a trend suggests that the use of emollients early in life as prevention of AD needs to be explored further. The more recent PREVENTADALL trial found that emollient therapy did not prevent AD by the age of 12 months.⁹⁴ With the understanding that emollients can minimize *S aureus* colonization,¹¹⁵ it would be interesting to evaluate if shifts in the skin microbiome occur with emollient therapy. To the best of our knowledge, there is no primary prevention targeting the skin microbiome; therefore, future studies are needed to determine the associated benefits and risks of targeting the skin microbiome in both current and developing studies.

Conclusion

In summary, we have outlined recent literature regarding the influence of the skin microbiome on allergic disease. We discussed how commensal-epidermal homeostasis influences allergic pathologic processes in commensal-epidermal homeostasis. Furthermore, we outlined the contributions of skin microbiome dysbiosis in the development of allergy and progression through the atopic march. Finally, we discussed how our improved understanding of the influence of the skin microbiome on allergy is being leveraged to develop therapeutic interventions to prevent the development and progression of allergy.

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