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On the Surface: Skin Microbial Exposure Contributes to Allergic Disease

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Abstract

Objectives: The skin microbiome modulates immunity by interacting with keratinocytes to combat pathogens. Allergic disorders are classified by IgE sensitivity and aberrant Th2 responses, and an increasing number of studies describe 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 PubMed.

Study Selections: Studies addressing relevant aspects of commensal-epidermal homeostasis, skin microbiome dysbiosis, and 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 anti-allergic Th1 and Th17 immunophenotypes within the skin and induce keratinocytes to secrete antimicrobial peptides and alarmins that enhance barrier function and antagonize pro-allergic 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 pathogen, *Staphylococcus aureus*. Fluctuations in the skin microbiome contribute to decreased barrier dysfunction, allergic sensitization, and Th2 cytokine secretion. Little is known about how the skin microbiome impacts food allergy, allergic rhinitis, and asthma, and it is poorly understood how cutaneous inflammation

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influences systemic allergic responses. Therapies are targeted towards maintenance of the skin barrier, replacement of healthy commensals, and anti-Th2 biologic therapy.

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

Keywords

Skin Microbiome; Allergy; Skin; Atopic Dermatitis; Asthma; Allergic Rhinitis; Food Allergy

Introduction

Allergic disorders, classified by IgE sensitivity, are steadily rising in prevalence worldwide and significantly impact 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 significant role in modulating allergic disorders. The microbiome is vital for immune system development 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. Lastly, 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 physiologic environments at each body site[2]. Body sites differ by pH, fatty acid composition, and ability of the skin to retain water, but can be influenced by gender, antibiotic treatment, and cosmetic use[3]. These factors in turn affect microbial ecology[3]. Site-specific microbial communities (Table 1) develop around three months of age[4], and early-life colonization is needed for the development of commensal tolerance and decreased risk of allergic diseases like 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 below, healthy commensal-epidermal homeostasis predominantly protects against allergic disease by promoting barrier function, deterring colonization of pro-allergic pathogens including *Staphylococcus aureus (S. aureus)*, and maintaining an anti-allergic Th1/Th17 immunophenotype.

Commensal-Epidermal Homeostasis: Epidermal Barrier-mediated Immunity— The skin consists of the dermis and epidermis (Figure 1), with the latter subdivided into

the 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 cross-linked structural proteins like filaggrin (FLG) are connected by corneodesmosomes, and a lipid-rich lamellar layer produced and secreted by keratinocytes[8,9]. TJs 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 below, disruptions in epidermal-microbiome homeostasis can compromise SC or TJ formation and function, thereby disrupting the skin barrier and increasing susceptibility to allergic disease.

Filaggrin: Mutations in *FLG*, or disrupted *FLG* expression or processing alters epidermal-microbiome homeostasis which can predispose microbial invasion[11], altered microbiome composition (i.e. reduced diversity)[12,13], increased susceptibility to viral and bacterial skin infections[14], and increased risk of allergic sensitization[15]. Reduced FLG levels and/or processing are major risk factors for allergic sensitization and allergic disease[16], and *FLG* expression is reduced by pro-allergic Th2 cytokines[1,11,17]. 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 lympho-epithelial Kazal-type-related inhibitor (LEKTI), encoded by *SPINK5*[18]. Reduced corneodesmosomes, reduced LEKTI, or unchecked KLK activity are associated with AD and other atopic diseases[19–21]. Indeed, individuals with Netherton Syndrome (NS), caused by *SPINK5* mutations, often exhibit AD, elevated IgE and varying degrees of asthma, food allergy and allergic rhinitis[19,20]. Individuals with NS are also susceptible to recurrent skin infections and dysbiosis, including infection by *S. aureus* which can further disrupt barrier function[22]. Finally, *S. aureus* phenol-soluble modulins (PSMs) enhance epidermal KLK activity and promote barrier dysfunction[23].

Stratum Corneum Lipids: The lipids of the lamellar layer include cholesterols, fatty acids (FAs) and ceramides[8,24] that may influence skin microbiome composition, skin barrier function and allergic disease susceptibility. FAs contribute to the acidic epidermal pH that favors commensals over pro-allergic bacteria[25]. Skin abundant in ceramides and long-chain FAs is associated with increased abundance of normal skin commensals, such as *Corynebacterium* and *Cutibacterium*[26]. Additionally, 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[8,24,25]. 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 Th2 cytokines can suppress FA elongase expression in human keratinocytes[28].

Tight Junctions: The importance of TJs as an epidermal barrier component highlighted by its frequent targeting for destruction by allergens and pro-allergic pathogens[29,30]. *S. aureus*,

for example, prevents TJ complex membrane localization, thereby reducing intercellular connectivity and increasing epidermal permeability[31]. TJ perturbations can further disrupt the SC by reducing FLG and lamellar lipid synthesis, and are associated with AD[32]. Contrarily, commensal *Staphylococcus epidermidis* (*S. epidermidis*) promotes TJ formation both directly and indirectly by inducing keratinocyte antimicrobial peptide (AMP) secretion (discussed below)[29].

Skin pH: The acidic 4–6 pH range of the healthy epidermis favors commensal over pro-allergic bacteria[25,33]. Contributors to this acidic pH are natural moisturizing factors (NMFs, which are byproducts of FLG catabolism) and FAs produced by keratinocytes or as metabolites of commensal bacteria (e.g. *Cutibacterium acnes*)[25,33]. This acidity antagonizes pathogens by several means, including reducing *S. aureus* keratinocyte adhesion and altering the conformation and activity of *S. aureus* virulence factors[25]. However, the inability to maintain acidic skin (e.g. defective FLG catabolism) alters microbial diversity and allows *S. aureus* keratinocyte adhesion[25,33], demonstrating the importance of skin pH in commensal-epidermal homeostasis.

Commensal-Epidermal Homeostasis: Keratinocyte-mediated Immunity—

Keratinocytes release a multitude of proteins that can impact commensal-epidermal homeostasis and thus influence allergic disease (Figure 2). Percutaneous allergens activate type 2 dendritic cells (DCs) and trigger the secretion of innate type 2 cytokines (thymic stromal lymphopoietin [TSLP], IL-33 and IL-25) from keratinocytes, which in turn stimulate canonical type 2 cytokine (e.g. IL-4) release from type 2 innate lymphoid cells (ILC2s). Together, allergen-activated DCs and ILC2-derived IL-4 co-stimulate the differentiation of naïve cells (Th0) into pro-allergic T-helper type 2 (Th2) cells[34–36]. The immune microenvironment of the skin is an important mediator of allergic disease susceptibility, and it is impacted by the commensal skin microbiome. It is beyond the scope of this review to comprehensively review skin immunity. A few key keratinocyte-derived factors are discussed here. Chief among them are AMPs and the alarmins S100A8 and S100A9, which are predominantly anti-allergic, and the innate type 2 cytokines, which are pro-allergic.

Antimicrobial Peptides: Human beta-defensins (hBDs) and cathelicidins (e.g. LL-37) are AMPs secreted by keratinocytes constitutively or in response to inflammatory or infectious stimuli[37–39]. These AMPs are active against many bacteria, fungi, and viruses[38,39] and primarily kill via membrane permeabilization, though other mechanisms have been described[37,39]. Bacterial and fungal skin commensals stimulate hBD or LL-37 secretion from keratinocytes which can synergize with antimicrobial compounds secreted from commensals to attenuate pathogen colonization[40,41]. hBDs and LL-37 can promote type 1 over type 2 immunity[38,39], though conflicting studies have observed pro-allergic activity in some contexts[39]. Finally, AMPs can increase epidermal barrier integrity by inducing TJs and promoting wound healing[38,39].

S100A8 and S100A9: The alarmins S100A8 and S100A9 are inflammatory mediators within the skin that function as either homodimers or as the heterodimer calprotectin[42]. Their expression is influenced by the skin microbiome; for example, commensal *S.*

epidermidis upregulates keratinocyte s100a8 and s100a9 expression by stimulating IL-17A secretion from commensal-specific Tc17 cells in mice[43]. Moreover, elevated calprotectin is associated with Th1 and Th17 inflammatory phenotypes[44]. S100A8 and S100A9 exert antimicrobial activity (e.g against *S. aureus)* by several means including the chelation of the essential metal ions Zn^{2+} and Mn^{2+} by calprotectin and S100A9-mediated neutrophil recruitment/activity[42]. Calprotectin also promotes skin barrier integrity by stimulating keratinocyte proliferation and differentiation[42].

Epithelial-derived Innate Type 2 Cytokines: The innate type 2 cytokines TSLP, IL-25 and IL-33 promote pro-allergic type 2 immunity through various mechanisms, including Th2 polarization, type 2 cell activation/expansion and type 2 cytokine induction[1,11,17]. These cytokines also induce barrier dysfunction directly by suppressing *FLG* expression[11,17]. Their influence on allergic disease is illustrated by their association with an AD-like phenotype if increased within the skin[11,17,45] and, for TSLP specifically, an asthma-like phenotype if it enters systemic circulation[46,47]. Various pro-allergic stimuli induce TSLP, IL-25 and IL-33 production, including type 2 cytokines, allergens, and mechanical damage[1,11,17]. 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 versus presence of normal commensals[48]. Pro-allergic *S. aureus,* on the other hand, induces TSLP and IL-33 expression by keratinocytes[49,50].

Commensal-Epidermal Homeostasis: Adaptive Immunity

Bacterial Microbiome: Just as in the gut, recent studies have demonstrated 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 type 1 and type 17 helper and cytotoxic T-cells (Th1, Th17, Tc1 and Tc17)[43,51,52]. Commensals induce these cells to secrete IL-17A which promotes keratinocytes to produce anti-allergic peptides such as s100a8 and s100a9[43]. Similarly, commensal *Corynebacteria accolens* can induce epidermal IL-17A+ γδ-T-cell influx, thereby promoting a type 17 immunophenotype[53]. Commensal-specific Tc17 T-cells can promote barrier integrity in mice directly by expressing tissue-repair genes and accelerating wound healing[51]. Interestingly, *S. epidermidis* can suppress *S. aureus* colonization when the skin barrier is intact, but when disrupted (e.g. tape-stripping) it instead promotes *S. aureus* colonization[54]. This phenomenon may be explained by a "poised" Th2 transcriptional profile identified within *S. epidermidis*-specific Tc17/Th17 cells which, upon exposure to pro-allergic innate type 2 cytokines, is translated, thereby superimposing or substituting the type 17 profile[55].

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 Th17 cells[56] and keratinocyte hBD production[57], which protects from allergy (see below). Contrarily, *Malassezia globosa* and *restricta* can promote pro-allergic TSLP release from keratinocytes[57], and *Malassezia*-specific IgE and Th2-polarized T-cells have been reported in AD patients[58]. Further study

is warranted to determine how fungal commensals influence allergic disease and if these effects are species- and/or context-dependent.

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 skin[59] (Table 1) and topical phage therapy reduced AD severity in one study, though the mechanism is unclear[60]. 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 10–20% of children worldwide, often in industrialized countries[61], with onset before one year of age in up to 60% of children[62]. Healthy and AD skin exhibit many structural and immunological differences. AD is also characterized by skin microbiome dysbiosis. However, whether these microbiome disruptions precede[63,64] or cause[13,26] skin disease or are a consequence of disease remains unclear. Studies suggest that commensals may play a role in preventing AD since commensal staphylococcal colonization at 2 months of age is associated with decreased AD incidence at one year[63] and commensals are positively correlated with the levels of long-chain FAs[12]. The loss of commensal abundance is correlated with individuals that have FLG deficiency[12]. Decreased commensal abundance is also observed during AD flares, but can be reversed with bleach baths, emollients, or topical steroids[65]. Birth cohorts suggest that infants who develop AD have a decrease in the heterogeneous commensal population [66], which is accompanied by increased abundance of the pathogen *S. aureus.* Infants with *S. aureus* colonization or lacking *S. aureus*-inhibiting commensals[67] at 3 months are more likely to develop AD compared to those who are not colonized[64].

Various *S. aureus* virulence factors have been associated with AD[68,69]. The *S. aureus* cell wall component lipoteichoic acid (LTA) upregulates over 300 genes in keratinocytes including Th2-polarizing genes such as TSLP and IL-4. In addition, LTA reduces FLG expression[70]. *S. aureus* also secretes enterotoxins capable of inducing inflammation by acting as superantigens and activating T cells via major histocompatibility complex II. Individuals with AD have significantly more specific-IgE to the *S. aureus* alpha, delta, and Toxic Shock Syndrome Toxin-1 toxins than healthy controls. *S. aureus*-derived PSMs can also increases keratinocyte KLK activity[23], which may promote *S. aureus* skin penetration by increasing desquamation and reducing barrier integrity (Figure 3).

Corynebacterium species are another common skin commensal (Table 1). Although *C. accolens* may protect from allergy by promoting IL-17A+ γδ-T-cell aggregation[53], *Corynebacterium* may be involved in allergic disease via the induction of type 2 responses[71]. *C. striatum* can increase expression of genes associated with *S. aureus* carriage in the nares, suggesting *C. striatum* promotes a shift towards *S. aureus* commensalism[72]. Several studies have demonstrated *Corynebacterium* presence in individuals with AD[73].

Malassezia species are common fungi on skin (Table 1) and healthy individuals have *Malassezia*-specific T-cells and antibodies[56]. However, AD subjects are characterized by the presence of *M. dermatis* and *M. sloofiae*[74], and several studies reveal the presence of

Malassezia-specific IgE[58] 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[75]. *Malassezia* exposure led to stratum corneum colonization, myelocytic infiltration, and IL-17 induction in mice[56]. This IL-17 induction was crucial to controlling fungal burden; however, *Malassezia* presence on the disrupted skin barrier induced inflammation, and IL-17-deficient mice showed a diminished inflammatory response *Malassezia* overgrowth[56]. These studies demonstrate that *Malassezia*-driven inflammation promotes AD-like disease in mice[56]. Studies are needed to characterize the differences, transition, or expansion of *Malassezia*-specific memory T-cells in healthy adults versus those with AD.

The skin microbiome also extends protection against viral pathogens[76]. Children with AD are prone 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 (HSV) which causes eczematicum herpeticum (EH). EH manifestations range from fever and malaise to encephalitis or septic shock and is recurrent in up to 25% of cases[77]. Viral infections are more likely in those with severe AD and often occur concurrently with *S. aureus* infections[77]. In fact, *S. aureus* alpha-toxin aids in HSV infection by promoting viral binding to keratinocyte receptors[78]. T-cell lines generated from individuals with EH showed increased secretion of IL-4^{+} when compared to T-cell lines generated from healthy controls, suggesting virus-specific T cells generate a type-2 response in EH[79]. Treatment of AD with topical corticosteroids did not prevent subsequent EH, nor did interferon-γ therapy result in symptom improvement[77].

Molluscum contagiosum is a common childhood viral infection caused by a DNA virus of the poxviridae family. While 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, while AD-induced pruritus promotes autoinoculation[80,81].

AD patients who had previously received a smallpox vaccination can develop eczema vaccinatum, characterized by disseminated vaccinia virus which, if systemic, is lethal[82]. FLG seems to protect from vaccinia, as *FLG*-deficient mice suffer from disseminated vaccinia infection[83]. 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[84].

Food Allergy—Food allergy affects approximately 1 in 13 children in the US and is defined as type-1 hypersensitivity to a given food antigen[85]. The LEAP/LEAP-ON study (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 significantly associated *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[86]. Further studies of the impact of the skin microbiome on food allergy are needed.

Allergic Rhinitis—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[87]. The nasal cavity harbors its own community of organisms to defend against environmental insults[88]. A study sampling *S. aureus* from both children and adults demonstrated that 85% of subjects were colonized with *S. aureus* in the nares, and approximately 77% of AD subjects colonized by *S. aureus* in the nares were also colonized on the skin[89]. These findings suggest *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[90]. A major risk factor for asthma development is allergic sensitization[61]. The absence of skin commensals and antimicrobial responses[91] predispose to microbiome dysbiosis, associated with inflammation and Th2 responses.

Organisms in household dust can be transferred to the skin via surfaces[92] and those sharing a household have been reported to have similar skin commensals[93], highlighting the influence of the environment on the skin microbiome. *S. aureus* persists in dust[94] and is highly abundant in the microbiome of purified house dust mite bodies[95]. Interestingly, *Staphylococcus*, *Haemophilus*, and *Corynebacterium* species in house dust are associated with increased asthma risk, while house dust levels of cockroach, cat, and mouse allergens are inversely related to asthma development in an early life cohort[96]. IgE sensitization to house dust mite [97] and *S. aureus* is common in those with asthma and/or AD[95], and percutaneous exposure to *S. aureus* via HDM 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 of the role the skin microbiome in allergic disease and the underlying mechanisms has revealed unique opportunities for targeted therapy (Figure 4).

Emollients

Although their utility in AD prevention has recently been cast into doubt[98], emollients are typically first-line therapy for AD, reduce the need for pharmaceutical interventions[99], and decrease AD severity[100]. Emollient administration increases bacterial diversity[100] and decreases *S. aureus* detection in lesional skin[101]. Coal tar emollients are an established AD therapy as they activate the aryl hydrocarbon receptor and thus induce keratinocyte differentiation, increase *FLG* expression, reduce Th2 responses, and decrease the abundance of pro-allergic *S. aureus*[102].

Emollients are also an efficient vehicle for other potential therapies, including those that specifically target the skin microbiome. Commensal- and keratinocyte-derived AMPs (e.g. hBDs and LL-37) prevent/reduce pathogen colonization[41,67]. Therefore, emollients combined with AMPs may be an effect treatment for allergic diseases. In fact, the application of emollients containing bacteria-derived *Sh*-lantibiotics to individuals with AD reduced detectable *S. aureus*[67]. Emollients containing keratinocyte AMPs may also be useful to treat biofilms, since LL-37 was able to eradicate pre-existing MRSA biofilms in a wounded skin model without compromising keratinocyte function[103]. 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[104]. 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[105]. Furthermore, the use of topical *R. mucosa* in individuals with AD demonstrated that the probiotic use was associated with decreased disease severity and *S. aureus* burden with no adverse events or treatment complications[106]. Oral probiotics have modest effects in those with moderate-severe AD, but little effect in those with mild disease[107]. It will be interesting for future studies to assess if *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 impact 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[108]. The human monoclonal antibody dupilumab blocks the IL-4 and IL-13 receptor and, thus, reduces their effector functions. The AD-LIBERTY EXPLORE study subjected moderate-severe AD patients to either weekly treatments of dupilumab or a control and found that subjects treated with dupilumab showed increased microbial diversity and decreased *S. aureus* in both nonlesional and lesional skin[109]. Additional studies are necessary to elucidate the underlying mechanisms and determine the impact on other organisms.

As discussed above, 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[1,11,17]. 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-severe AD. Etokimab reduced AD severity by over 50% with only minimal adverse effects[110]. Although the trial did not directly examine etokimab's impact on *S. aureus* colonization, anti-IL-33 therapy may be a 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 prior to the presentation of AD symptoms making the microbiome a potential diagnostic tool. Unfortunately, although the influence of pathogens on atopy has been demonstrated[64,66,69,111–113], there are obstacles preventing the efficient, cost-effective, and reliable use of the microbiome for diagnostic purposes[114]. Currently, metagenomic analysis is expensive, non-quantitative, and difficult to interpret in a clinical laboratory setting, making it a poor diagnostic tool[115]. Additionally, despite the fact that *S. aureus* colonization has been associated with increased AD severity in many studies[7,116], *S. aureus* colonization status does not influence current clinical practice[62].

Primary prevention of AD is focused on maintenance of the skin barrier. The Barrier Enhancement for Eczema Prevention (BEEP) trial and the Prevention of Eczema By a Barrier Lipid Equilibrium Strategy (PEBBLES) 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[117,118]. The PEBBLES trial is distinguished by the use of an emollient based on the ratio of ceramides, cholesterol, and fatty acids[118]. 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[98]. With the understanding that emollients can minimize *S. aureus* colonization[119], it would be interesting to examine if shifts in the skin microbiome occur with emollient therapy. To our knowledge there are no primary preventions 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.

Conclusions

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. We then 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 skin microbiome's influence of allergy is being leveraged to develop therapeutic interventions to prevent the development and progression of allergy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations/Acronyms:

AD	Atopic Dermatitis
AMP	Antimicrobial Peptide
AR	Allergic Rhinitis
DC	Dendritic Cell
EH	Eczematicum Herpeticum
FA	Fatty acid
FLG	Filaggrin
hBD	Human Beta-Defensin
HDM	House dust mite
HSV	Herpes Simplex Virus
ILC	Innate Lymphoid Cell
IgE	Immunoglobulin E
LEKTI	Lympho-epithelial Kazal-type-related Inhibitor
LTA	Lipoteichoic Acid
NMF	Natural Moisturizing Factor
NS	Netherton Syndrome
PSM	Phenol-Soluble Modulin
SC	Stratum Corneum
SG	Stratum Granulosum
Th1	T-helper 1 Cell
Th2	T-helper 2 Cell
Th17	T-helper 17 Cell
TJ	Tight Junctions
TSLP	Thymic Stromal Lymphopoietin

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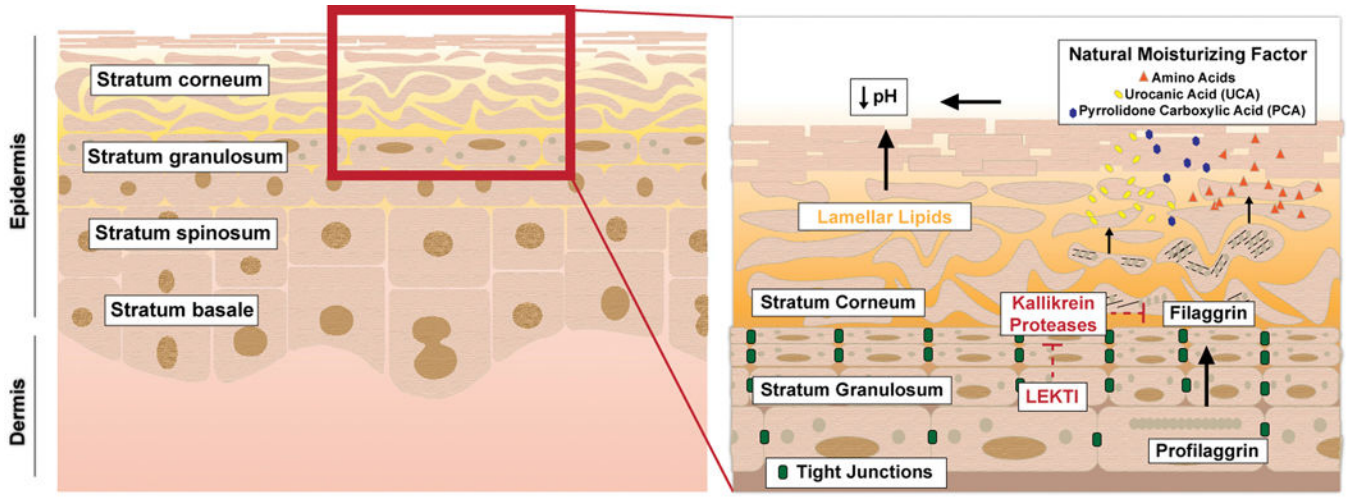

Figure 1. Properties of the epidermal barrier.

The skin consists of a dermis and epidermis, which is further subdivided into the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum. The epidermal barrier is formed primarily by (a) tight junctions within the stratum granulosum and (b) the stratum corneum. The stratum corneum consists of lamellar lipids (e.g. ceramides and long-chain fatty acids) and a cornified envelope. Natural moisturizing factors (byproducts of filaggrin catabolism) and fatty acids of the lamellar layer create an acidic pH. Kallikrein proteases (KLKs) promote desquamation by degrading filaggrin and corneodesmosomes. The KLKs are inhibited by LEKTI.

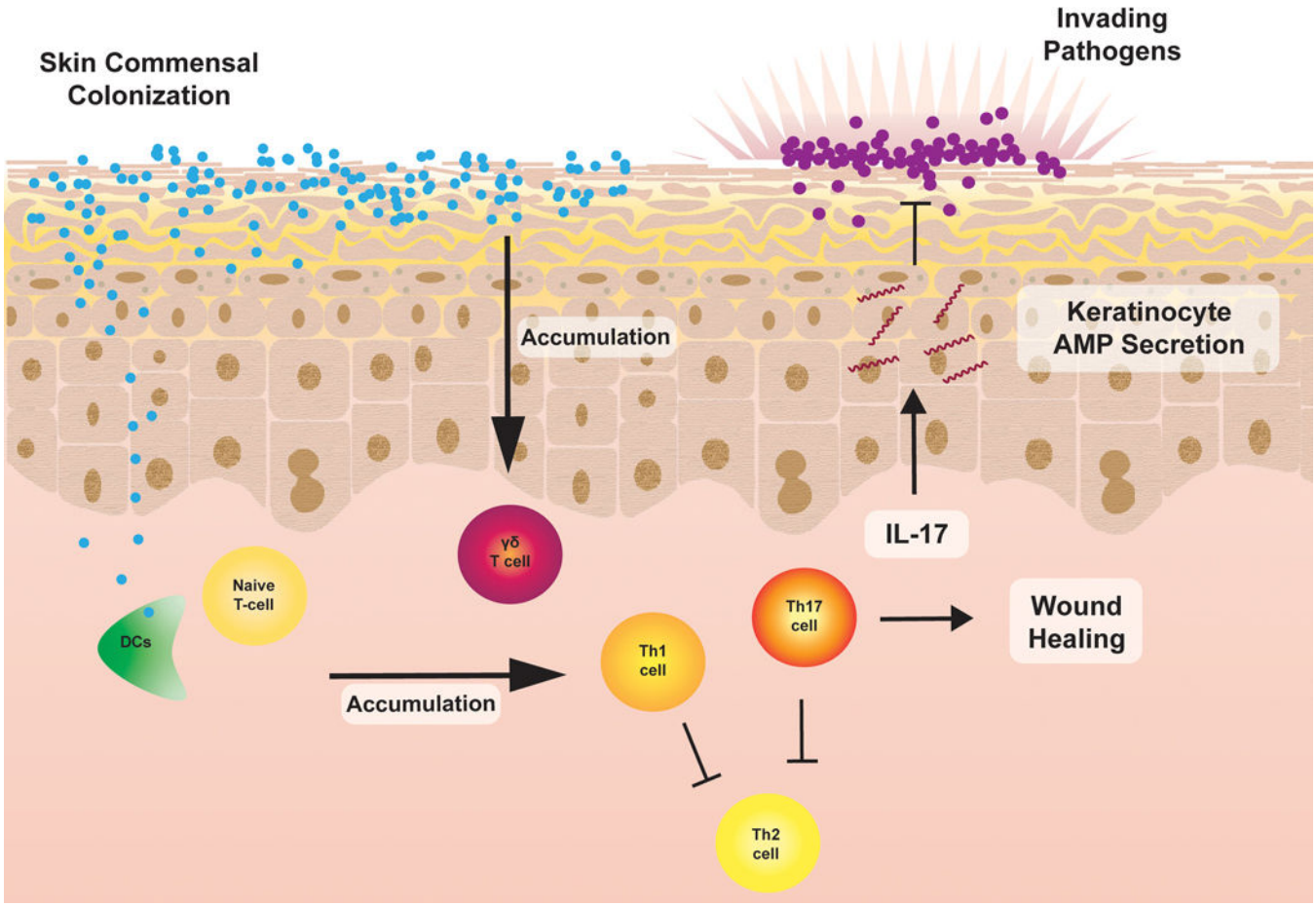

Figure 2. Adaptive Immunity in Commensal-Epidermal Homeostasis.

Commensals induce the accumulation of γδ-T-cells and commensal-specific type 1 and type 17 T-cells. These cells protect against allergic disease by suppressing type 2 immune responses, promoting wound healing, and inhibiting pathogens by secreting IL-17 which induces keratinocyte antimicrobial peptide secretion.

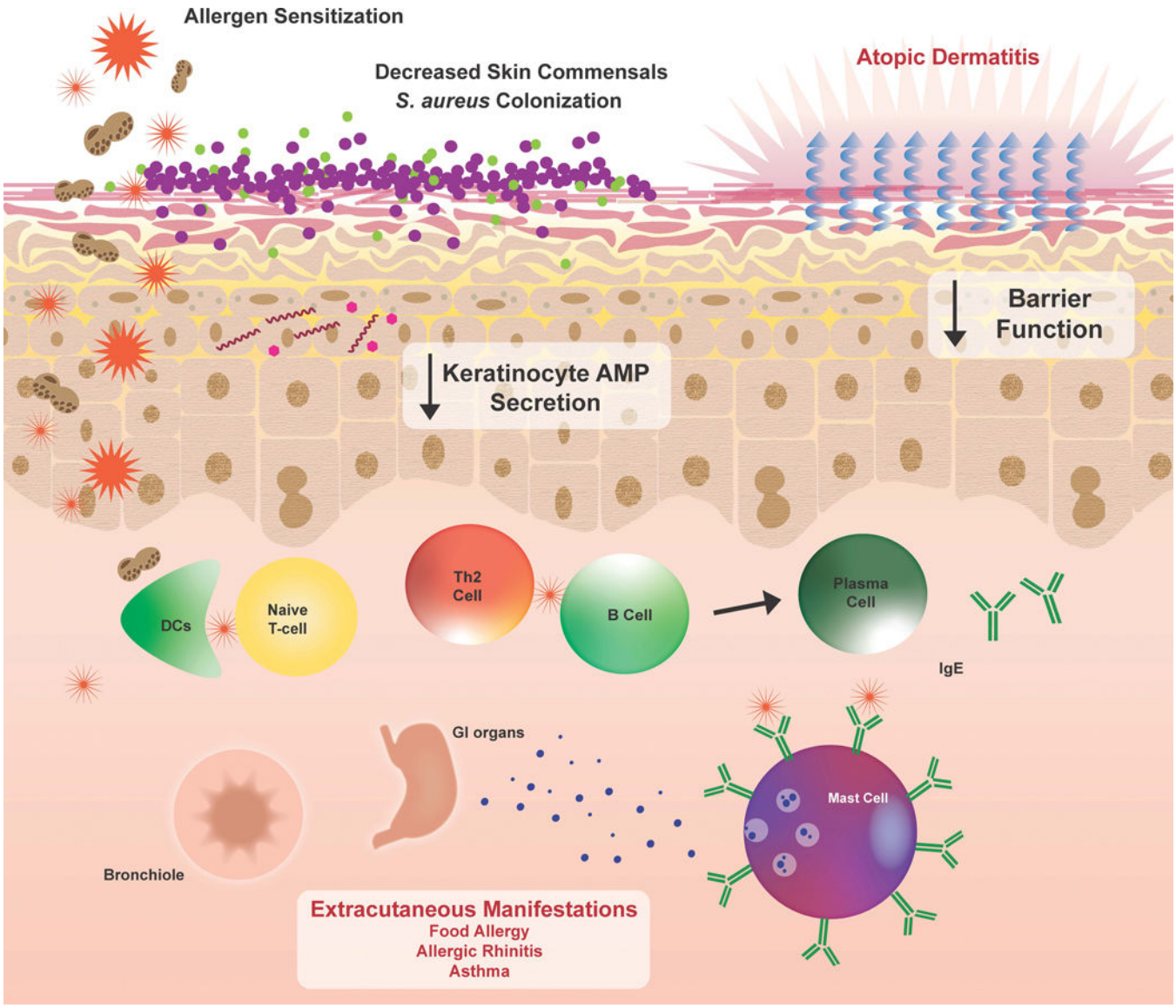

Figure 3. Effect of the skin microbiome on allergic disease.

A decrease in skin commensals and the presence of pathogens contributes to skin microbiome dysbiosis that can occur in allergic disease. Decreases in keratinocyte AMPs also prevent clearance of these pathogens. In particular, *S. aureus* is shown to decrease barrier function, induce IgE production, and induce secretion of Th2 cytokines, which can have systemic consequences and exacerbate extracutaneous manifestations of allergy.

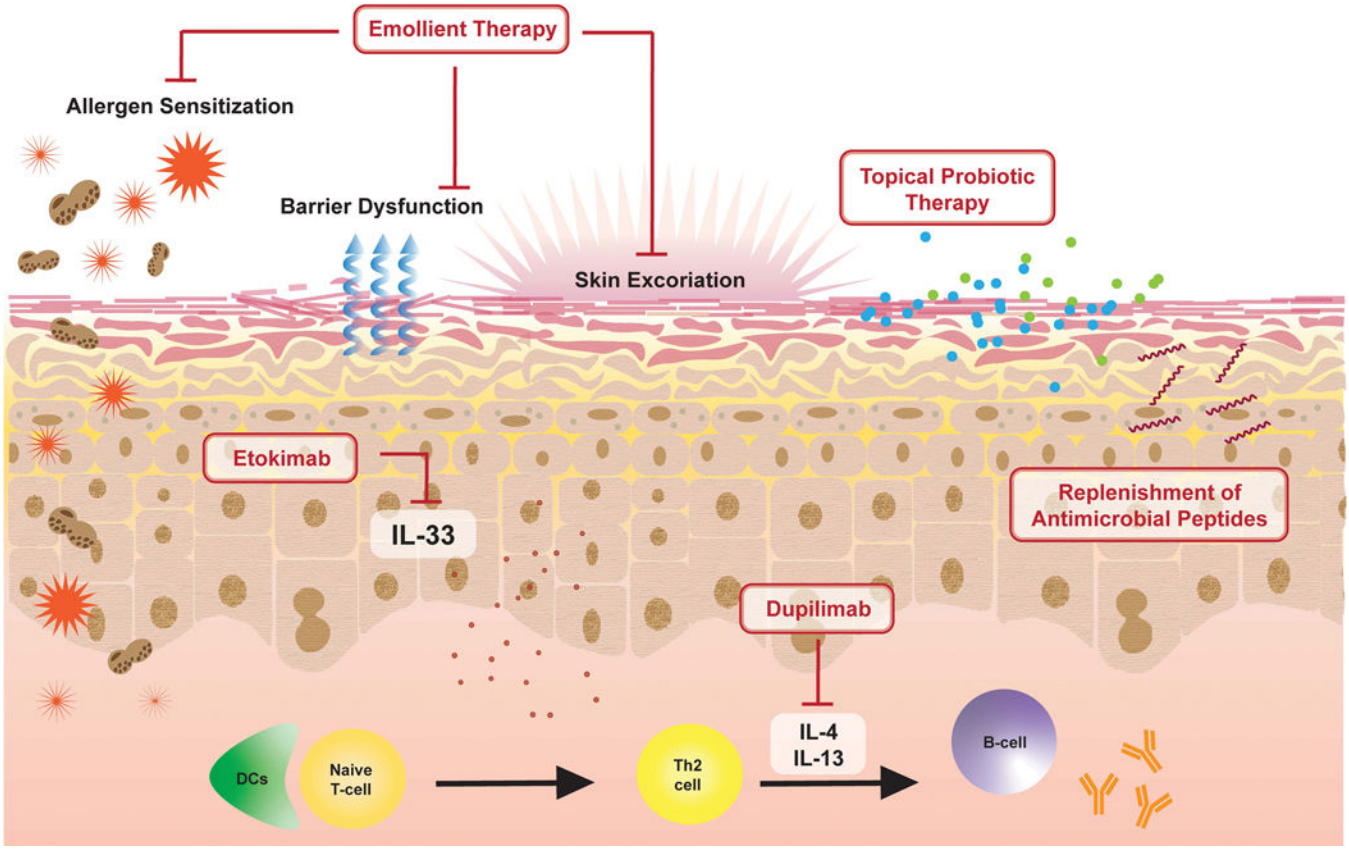

Figure 4. Interventions influencing the skin microbiome.

Emollient therapy aids in repairing a damaged skin barrier preventing inflammation and sensitization. The replacement of skin commensals and antimicrobial peptides are 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.

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*		33, 4, 105, 106
		Cutibacteria[*]	*C. acnes*	
	Firmicutes	*Staphylococci*	*S. epidermidis*	
	Proteobacteria	*Roseomonas*	*R. mucosa*	
Skin Mycobiome	*Basidiomycota*	*Malassezia*	*M. furfur, M. restrica, M. globosa, M. sympodialis*	56
	Ascomycota	*Candida*	*C.albicans*	
Taxa				
Skin Virome	Phages:	*Pseudomonas* phage, *Bacillus* phage, *Staphylococcus phage, Propionibacterium* phage, *Planktothrix* phage, *Streptococcus* phage, *Burkholderia* Phage, *Mycobacterium* Phage		59, 60
	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*	65, 72, 113
	Firmicutes	*Staphylococci*	*S. aureus*	
		Streptococci	*S. pyogenes*	
Skin Mycobiome	*Basidiomycota*	*Malassezia*	*M. dermatis, M. sloofiae, M. sympodialis*	74, 75
	Ascomycota	*Candida*	*C. albicans*	
Taxa				
Skin Virome	*Herpesviridae*	*Herpes Simplex Virus*		113
	Poxviridae	*Molluscum contagiosum, Vaccinica Virus*		

[*] Formerly *Propionobacteria*