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REVIEW ARTICLE

The skin microbiome in pediatric atopic dermatitis and food allergy

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Abstract

The skin microbiome is an extensive community of bacteria, fungi, mites, viruses and archaea colonizing the skin. Fluctuations in the composition of the skin microbiome have been observed in atopic dermatitis (AD) and food allergy (FA), particularly in early life, established disease, and associated with therapeutics. However, AD is a multifactorial disease characterized by skin barrier aberrations modulated by genetics, immunology, and environmental influences, thus the skin microbiome is not the sole feature of this disease. Future research should focus on mechanistic understanding of how early-life skin microbial shifts may influence AD and FA onset, to guide potential early intervention strategies or as microbial biomarkers to identify high-risk infants who may benefit from possible microbiome-based biotherapeutic strategies. Harnessing skin microbes as AD biotherapeutics is an emerging field, but more work is needed to investigate whether this approach can lead to sustained clinical responses.

KEYWORDS
atopic dermatitis, food allergy, microbiota, skin microbiome, *Staphylococcus aureus*

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin condition characterized by disrupted skin barrier function and immune dysregulation. Its onset is typically in early life and is more common in children, afflicting up to 25%.[1] AD is a complex disease with a multifaceted burden encompassing physical discomfort, sleep disturbances, limitations in daily activities and

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exerts a profound psychosocial impact on children and their caregivers.[2]

In addition to these challenges, children with AD often experience multiple co-morbidities such as food allergies (FA), allergic rhinitis, asthma, autoimmune disorders and recurrent skin infections.[3,4] The pathogenesis of AD in children involves a complex interplay of genetic factors, skin barrier defects, Th2 cytokine imbalances, allergen sensitization and microbial interactions.[5]

In particular, early onset and severe AD are significant risk factors for the development of FA in children. Lack et al. first proposed that allergen exposure through the skin rather than through the oral route, during a critical period in early life, can lead to the development of FA, whereas early consumption of allergenic food proteins induces oral tolerance.[6] This has since become widely known as the 'Dual Allergen Exposure Hypothesis'. The concept of primary prevention of AD has thus gained traction as a strategy to mitigate transcutaneous sensitization and subsequently reduce the risk of FA and other allergic disorders in the 'atopic march'.

The skin, being the largest organ in the human body, plays a vital role in providing barrier protection, sensory regulation and immune and thermal homeostasis.[7] It is colonized by an extensive community of bacteria, fungi, mites, viruses and archaea thought to interact with the host to influence health and disease states.[8] Recent advances in sequencing technology revealing a diverse skin microbial community on healthy skin and increasing microbial-host interaction studies in humans and model systems suggest a fine equilibrium exists among pathogens, commensal organisms and the immune system. However, in children with AD, this skin microbiome is altered.

This review highlights the known mechanistic pathways involved in the development of AD and FA in children, as well as the emerging understanding of the role of the skin microbiome in pediatric AD and FA. It also discusses recent studies exploring the potential of the skin microbiome in the treatment and prevention of these conditions.

2 | SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed, Cochrane Library and Medline for papers published between January 2012 and December 2022, using the following terms: 'skin microbiome', 'bacteria', '*Staphylococcus aureus*', 'fungi', 'mites', 'viruses', 'archaea', 'atopic dermatitis', 'eczema' and 'food allergy' in combinations. Articles were also identified through searches of reference lists of selected key papers in the field. The search was not limited by language. The final reference list was selected on the basis of originality, up-to-dateness, impact in the field and relevance to the broad scope of this review.

3 | SKIN MICROBIOME IN AD

AD is characterized by a waxing and waning course, in which worsening of AD lesions (flares) occur periodically followed by a period of clinical improvement with treatment.[5] Microbes on the skin are thought to play an important role in skin homeostasis by modulating the immune system,[9] providing colonization resistance against pathogens,[10] or, in the case of *S. aureus*, exacerbating skin inflammation.[11] The skin microbiome composition changes dramatically across the AD flare cycle, with microbial diversity dropping as disease severity increases and a concomitant increase in abundance of *S. aureus* in the majority of cases.[12] Predominant *S. aureus* strains are often observed in the flare state, while heterogenous *Staphylococcus epidermidis* strain communities are seen in both the flare and post-flare states. On non-flare AD skin, microbial diversity remains high; however, the composition and functional potential of the AD subjects' microbiome are distinct from healthy individuals, highlighting potential microbiome-related factors that could increase the susceptibility to flares.[13] This altered microbiome signature in the non-flare skin of AD patients is more pronounced in individuals with high levels of circulating IgE and also associates with molecular changes in the skin surface microenvironmental niche.[14] There is growing evidence that commensal microbes may play a mechanistic role in skin barrier repair and attenuate inflammation during AD via AhR-dependent signalling and glucocorticoid-related pathways.[15,16]

The predominance of *S. aureus* strains in flares and relative reduction of commensal microbes are linked with skin barrier disruption and inflammation in AD skin.[17] A meta-analysis reported that around 70% of individuals across all ages with AD are colonized with *S. aureus* on lesional skin, 30%–40% in non-lesional skin and 62% in the nares.[18] AD patients have significantly higher odds of *S. aureus* colonization than healthy controls at all sites compared.[18]

There is a need for a greater understanding of the initiators and drivers of the altered skin microbiome and why *S. aureus* predominates on AD skin. The contribution is likely complex and multifactorial, driven by Th2 skewing of the immune milieu, disruption to the skin barrier by mutations in genes such as *FLG* and alterations in lipid and protein production in the epidermis that increase *S. aureus* adherence.[19–21] There is also strong evidence from genetic disorders that either impact the immune system (such as inborn errors in immunity) or disrupt skin barrier function (such as congenital ichthyosis), resulting in the overrepresentation of *Staphylococcus* species as a common feature in microbial communities.[22,23] Thus, both host and microbiome factors likely contribute to AD pathogenesis in susceptible individuals.

Staphylococcus aureus has long been associated with AD[24] and shown to demonstrate its pathogenic effects through various mechanisms such as disruption of barrier integrity, intrinsic host immune dysregulation and expression of virulence genes. (Figure 1) Virulence factors such as α-toxin, protein A (SpA), lipotechoic acid (LTA), phenol soluble modulin (PSM)-α and proteases can damage keratinocytes.[25,26] Several studies have identified microbial characteristics which may contribute to AD severity.[21,27,28] Overgrowth of *S. aureus*, particularly clonal strains, were seen in patients with more severe disease.[21,27] AD-associated *S. aureus*

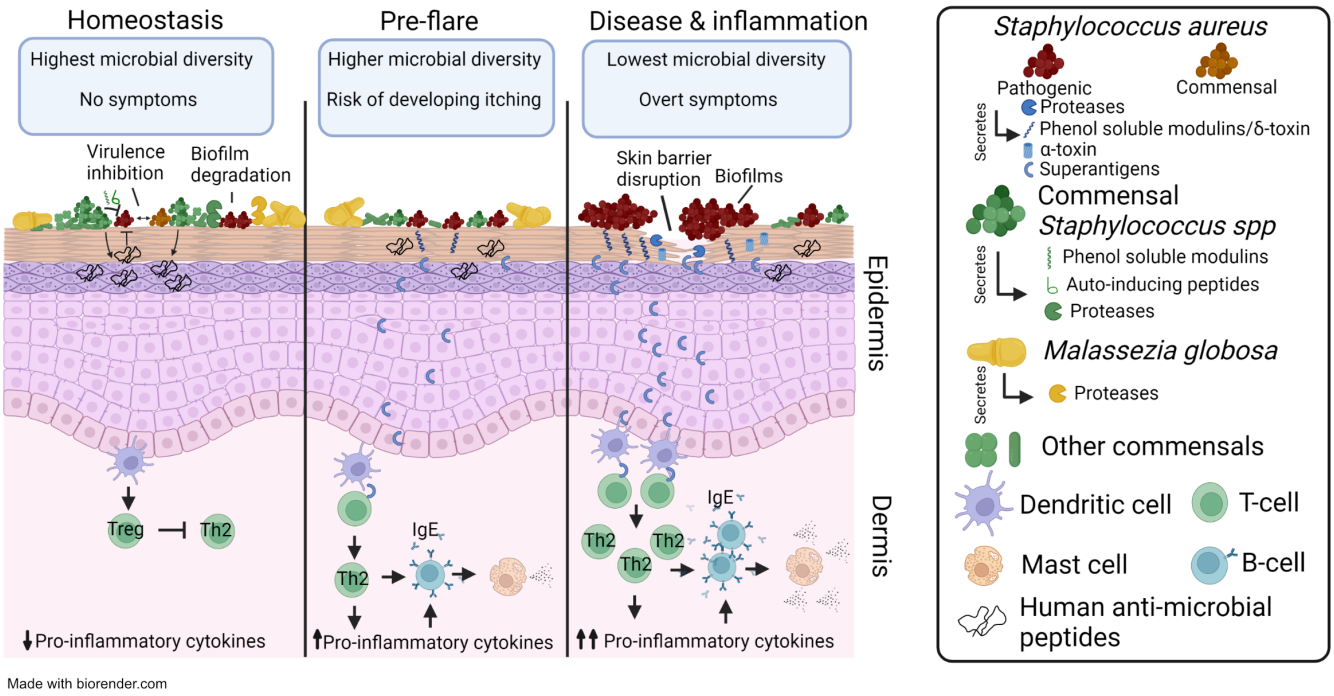

FIGURE 1 Interactions between *Staphylococcus aureus*, native skin commensals and host cells in healthy or diseased skin. On healthy skin (left), commensals like coagulase-negative *Staphylococcus* (CoNS) and the fungi *Malassezia* secrete a variety of compounds to inhibit the growth of the pathogen *Staphylococcus aureus* (*S. aureus*). CoNS secrete phenol soluble modulins (PSMs) and auto-inducing peptides, which inhibit *S. aureus* growth and virulence factor expression respectively. CoNS can stimulate host epidermal cells to produce anti-microbial peptides (AMPs) to further restrain *S. aureus* growth. Both CoNS and commensal *Malassezia* also secrete a variety of proteases, which disrupt *S. aureus* biofilm formation. These mechanisms contribute to T cell tolerance and likely optimize barrier function on healthy skin. It is however unclear if these proteases may also disrupt the host barrier to some extent. On inflamed skin (right), increased *S. aureus* colonization and biofilm formation can lead to heightened secretion of virulence factors such as PSMs, toxins and proteases that damage the stratum corneum. Host AMPs are present in lower amounts or are rendered less effective due to *S. aureus* activity and Th2 signalling. *S. aureus* can also suppress the growth or activity of skin commensals. Superantigens released by *S. aureus* can penetrate the epidermis and trigger dermal dendritic cells to drive T helper 2 (Th2) polarization and expansion. Excessive numbers of Th2 cells, in turn, produce a variety of pro-inflammatory cytokines, which further exacerbate skin barrier dysfunction, IgE production by B-cells and mast cell degranulation. While the pre-flare skin (middle) is not inflamed, there might be decreases in the abundance of commensals which inhibit *S. aureus*, potentially promoting the transition to a pathogenic state. These individuals have elevated Th2 responses and IgE compared to healthy skin, and are predisposed to severe itching in subsequent flares. (Created with BioRender.com).

strains were also enriched in virulence factors.[28] In contrast, distinct strains of *S. epidermidis* were found in patients with less severe disease.[21,28]

Viral-host interactions also mediate AD morbidity. AD patients with a history of *S. aureus* skin infections are at greater risk of eczema herpeticum (EH), a severe blistering cutaneous infection caused by herpes virus.[29,30] Some mouse and in vitro studies have raised the possibility that *S. aureus* strains which produce staphylococcal toxic shock syndrome toxin-1[31] or α-toxin[32] may enhance viral entry. Conversely, AD host factors such as genetics, immune dysregulation and barrier defects also increase susceptibility to EH compared to healthy individuals.

Differences in fungal composition have also been described in AD. Cross-sectional sequencing studies demonstrated lower relative abundances of *Malassezia* spp. Correspondingly, the higher prevalence of non-*Malassezia* fungi such as *Cladosporium*, *Alternaria* and *Aspergillus* in AD skin[13,33] may be attributed to environmental selection pressures as *Malassezia* spp. grow best in lipid-rich conditions, which are deficient in AD skin. Certain *Malassezia* species perform protective functions, whereas others may induce skin inflammation.[34,35] A small study ($n = 17$) demonstrated that *Malassezia globosa*, a commensal yeast from healthy adult volunteers, secretes a protease (*Malassezia globosa* Secreted Aspartyl Protease 1—MgSAP1) which has been shown through in vitro culture and biochemical assays to disrupt *S. aureus* biofilms by hydrolyzing SpA.[34] The impact of these proteases on the host barrier itself is, however, unclear. A murine AD model showed that *M. pachydermatis*, *M. sympodialis* and *M. furfur* activated IL-23 and IL-17 inflammatory pathways, and this was corroborated by the presence of *Malassezia*-specific production of these cytokines by memory T cells in adult AD patients.[35] These targeted studies were designed to investigate the specific inflammation-associated mechanisms exerted by commensal *Malassezia* spp., mostly in in vitro or in vivo models. There remains little direct data on how yeast interacts with other skin microbiota or influences human host responses.

Native skin commensals also form part of the innate host defence against pathogenic organisms. *S. epidermidis* and *Staphylococcus hominis* are examples of coagulase-negative staphylococci (CoNS) which stimulate host production of antimicrobial peptides like cathelicidin and human beta-defensin (HBD), and also directly produce PSM-γ and PSM-δ, which inhibit the growth of pathogenic bacteria.[36]

An observational sequencing study ($n = 100$ adult patients) detected increased abundances of the *Demodex folliculorum* mite on AD skin compared to healthy controls.[37] However, no further mechanistic studies were done to assess the role of *Demodex* mites in inducing or perpetuating skin inflammation in these patients. While house dust mites have been shown to trigger inflammation in AD-like murine models,[38] there is little data to show that they trigger flares in AD patients. There is thus insufficient evidence to conclude if skin mites play a major role in AD development.

4 | SKIN MICROBIOME MARKERS OF AD IN EARLY LIFE

Early life exposure to the external environment may shape host–microbe interactions that play roles in skin health and atopic disease onset.[39] Distinct fluctuations in neonatal and infant skin physiology in the first year of life influence skin microbiota colonization patterns. The skin microbiome in healthy neonates is characterized by the predominance of *Bacillota* (formerly *Firmicutes*), such as *Staphylococcus* and *Streptococcus*, and fewer *Actinomycetota* (formerly *Actinobacteria*) (*Cutibacterium* and *Corynebacterium*). A small, open, non-randomized, cross-sectional study found that soon after delivery, vaginally born neonates ($n = 4$) have skin microbiota that is similar to their mothers' vaginal fluid, predominantly *Lactobacillus* or *Prevotella* spp., while neonates born through Caesarean section ($n = 6$) acquire mainly maternal skin commensals such as *Staphylococcus*, *Corynebacterium and Cutibacterium* spp.[40] In a subsequent publication where infants were followed up to 30 days of life, the authors reported that four Caesarean-born infants who were exposed to their mothers' vaginal fluids at birth continued to exhibit skin microbiota characteristics similar to vaginal-born infants.[41] A larger follow-on observational study recruited n = 98 vaginal-born infants and $n = 79$ Caesarean-born infants, 30 of whom were swabbed with maternal vaginal fluids after birth. Caesarean-born infants who underwent vaginal seeding had a gut microbiota developmental trajectory up to age 12 months that more closely resembled vaginal-born infants, compared to those who were not seeded, suggesting that early life vaginal microbiota transfer had sustained differences up to 1 year post-intervention.[42] A subsequent double-blind randomized controlled trial of 10 vaginal-seeded infants versus 10 controls (seeded with sterile saline) found that vaginal-seeded infants had significantly reduced alpha diversity in the skin at Day 1, as well as in transitional stool up to Day 30 of life.[43] There has, however, been no longitudinal data beyond 1 year of life, nor any data on whether this intervention had any impact on infant disease outcomes including AD. Furthermore, as the Caesarean sections were all elective and non-emergent, there is little known about how other peripartum factors may influence maternal and infant microbiota and maternal–infant transmission.

Various factors such as maternal microbiome, mode of delivery and early environmental exposure may influence the maturation trajectories of the infant skin microbiome, and from murine models, potentially infant skin immunology as well. A systematic review by Xiong et al. found that studies examining the link between mode of delivery and AD risk harboured significant heterogeneity that could be attributed to differences in country, study design and method of AD ascertainment.[44] No definite conclusions can thus be made about the impact of delivery mode on AD risk.

Several longitudinal studies have demonstrated early skin microbial signals that may be predictive of AD onset. A small longitudinal study, nested within a birth cohort, found that infants who developed AD at age 1 year ($n = 10$) had a much lower abundance of commensal *Staphylococcus* species detected by 16S rRNA gene sequencing at 2 months of age relative to controls ($n = 10$).[45] A larger prospective birth cohort study ($n = 146$) found that early *S. aureus* colonization (by culture-based methods) in the first few months of life appeared to precede the onset of AD in infants.[46] Nakamura et al. further observed that infants in the Chiba birth cohort who had *S. aureus* strains harbouring dysfunctional mutations in their *Agr* quorum-sensing (QS) system did not go on to develop AD ($n = 24$), postulating that this functional *S. aureus* virulence mechanism may be important for AD pathogenesis.[47] Further studies are needed to examine the mechanistic pathways through which early differences in microbiota composition may influence later disease onset, such as the impact of microbiota on host immunological responses, skin barrier protein expression and barrier function.

Exposures to environmental influences, such as farming, air pollutants and epithelial irritants have been associated with increased risks of AD and/or FA in early life. In the South African Food Allergy (SAFFA) cohort, exposure to farm animals in infants and their mothers during pregnancy was protective against food and aeroallergen sensitization in rural infants.[48] The Wisconsin Infant Cohort Study (WISC) cohort likewise observed a reduced incidence of AD in farm-dwelling infants compared to those not living on farms, particularly in those who had more diverse and numerous animal exposures.[49]

The Netherlands' Prevention and Incidence Asthma and Mite Allergy (PIAMA) birth cohort found that long-term exposure to traffic-related air pollution was associated with food allergen sensitization at age 4 years.[50] Another meta-analysis found that passive smoking exposure was associated with an increased risk of FA and allergic dermatitis in children.[51] It has been postulated that air pollutants may induce skin barrier damage through various mechanisms such as triggering oxidative stress, epigenetic modifications and immune dysregulation.[48,52] Detergent use has also been

shown to disrupt skin barrier function by damaging tight junctions and triggering pro-inflammatory responses.[53] These early life environmental exposures, however, did not investigate host microbiota changes in relation to AD and FA outcomes.

Marked pubertal differences in the skin microbiome have been demonstrated as children sexually mature through Tanner stages.[54,55] Similarly, the skin microbiome composition of young children with AD (2–12 years, $n = 59$) differed from adolescents (13–17 years, $n = 13$) and adults (18–62 years, $n = 56$) versus age-matched nonatopic healthy controls. Skin microbiome diversity was significantly higher in the non-lesional skin of AD children than in adolescents/adults, corresponding to similar patterns in healthy individuals.[56] However, *Staphylococcus* was significantly more abundant in lesional as well as non-lesional skin of children and adolescents with AD. Skin commensals for AD and control subjects were also age-specific: such as *Streptococcus* spp. enriched in children compared to *Cutibacterium* and *Corynebacterium* in adults.

There are only a few observational studies describing changes in skin microbiome signatures in early infancy that may be associated with AD onset. Further mechanistic studies are needed to deconvolute the potential role of the skin microbiota in AD pathogenesis and their interactions with the host skin barrier and immune system in the pre-clinical disease state.

5 | ANTIBIOTIC USE AND SKIN MICROBIOME

There has been some evidence from meta-analyses for the link between antibiotic use in pregnancy ($n = 18$ studies)[57] and early life ($n = 22$ studies)[58] and infant AD. These studies varied considerably in design, ranging from cohort studies to case–control studies and retrospective medical record reviews, yielding high heterogeneity. Wan et al.[57] in particular showed that significant links were demonstrated only for retrospective studies but not for prospective or cross-sectional studies, suggesting that a degree of ascertainment bias may exist. Confounding by indication may also be present in studies where the indication for antibiotic prescriptions may be due to early skin disease or infections. The meta-analyses were also not able to delineate the specific at-risk window in pregnancy or early life where antibiotic administration might conclusively increase the risk of infant AD.

It has also been shown that the skin microbiome in healthy adults receiving antibiotic treatment manifested greater changes, as demonstrated by increased Bray-Curtis dissimilarities after treatment compared to baseline.[59] Longer antibiotic courses induced more profound and persistent changes, suggesting that there was also a dose/duration-dependent effect.

Antenatal, perinatal and postnatal antibiotic exposure may theoretically likewise cause perturbations in the host microbiome and this has been demonstrated in gut microbiome studies.[60] A few database studies have described an association between early antibiotic exposure and AD; however, there is limited data describing the direct impact of maternal antibiotic exposures on their infants' skin microbiome and its potential impact on infant AD.[61,62] Hence, definitive conclusions on whether the skin microbiome plays any role in the link between antibiotic exposures in pregnancy, early life and adulthood on AD outcomes cannot be made.

6 | SKIN MICROBE TRANSMISSION IN HOUSEHOLDS OF PEDIATRIC AD PATIENTS

Besides lesional sites of AD, the anterior nares and inguinal creases are common reservoirs of *S. aureus*. Clinical studies have shown that *S. aureus* strains can be shared between the reservoirs and distal skin sites, indicating that skin microbes are spread through physical transfer or by the airborne route.[63,64] The seeding of *S. aureus* between reservoirs and other body sites may promote recolonization, disrupting optimal AD control.

There is also growing appreciation for the importance of other non-self-reservoirs and skin microbial transmission between individuals in close contact in perpetuating AD. Studies utilizing whole genome sequencing of skin microbiomes have further demonstrated a general sharing of skin microbes apart from *S. aureus* between members of the same household.[64] In a cross-sectional study of 30 primary caregiver-child pairs (children aged 4–10 years) in households with pediatric AD and the same number of age-matched control pairs, Chia et al. demonstrated significant microbiome similarities between the skin of clinically healthy caregivers and the skin of their children.[64] The *S. aureus* to *S. hominis* ratio within skin microbiomes was a more sensitive and specific marker for an individual's (caregiver or child) affiliation to a house with an AD patient than just *S. aureus* relative abundances alone. Further studies involving prospective cohorts are necessary to establish stronger evidence for the role of intra-familial microbial transmission in the onset, progression and recurrence of pediatric AD.

Taken together, the current literature supports further investigations into whether clinically healthy household members should also undergo decolonization to manage recurrent pediatric AD. A clinical trial has shown that both *S. aureus* decolonization of all household members of children below 18 years of age (median age 3.9 years, range, 1.1–17.1 years) with community-acquired methicillin-resistant *S. aureus* (MRSA) skin and soft tissue infections (SSTI) or individualized decolonization of only household members with history of SSTI had a modest effect on the risk of study participants developing future SSTI,[65] but no trial has been conducted in the context of recurrent pediatric AD to date. The ineffectiveness of these household decolonization strategies could be due to the lack of decontamination of household surfaces and fomites, which are significant reservoirs of *S. aureus*, or due to potential complexities with re-acquisition of *S. aureus* from sources outside the household. More comprehensive decolonization regimes will need to be trialled to evaluate the efficacy of expanding

treatment beyond the index patient for managing recurrent pediatric AD.

7 | SKIN MICROBIOME CHANGES IN AD TREATMENT

Treatment of AD flares reduces disease severity and decreases *S. aureus* relative abundances with concomitant increase in skin microbiome diversity including commensal skin flora such as *Corynebacterium and Cutibacterium*.[12] Topical corticosteroids and bleach baths have also been associated with cutaneous microbiota composition on lesional skin temporarily resembling baseline or similar to non-lesional skin, although their microbiota remained distinctly different from healthy control skin.[66,67]

More recent therapies have targeted specific inflammatory pathways. The Th2 inflammatory axis plays a key role in AD pathology.[5] During AD pathogenesis, Th2 polarization leads to increased expression of the cytokines IL-4, IL-13 and IL-31.[68,69] These trigger proinflammatory responses promoting pruritus, reduced epidermal barrier function, increased transepidermal water loss and skin inflammation. Skin barrier defects facilitate the binding of *S. aureus*, while Th2 cytokine signalling inhibits anti-microbial peptide secretion by keratinocytes,[19] potentially contributing to a vicious cycle of sustained inflammation in chronic AD.

One of the biologics targeting components of the Th2 inflammatory axis is dupilumab, a monoclonal antibody which blocks IL4 receptor alpha (IL-4Rα), leading to inhibition of IL-4/IL-13 signalling. Numerous clinical trials have shown that dupilumab is effective in alleviating AD symptoms and reduction in disease scores,[70] and has been approved by the FDA for this purpose in both adults and children.[71]

Dupilumab therapy has been associated with skin microbiome composition alterations. One double-blind, placebo-controlled clinical trial conducted by Callewaert et al. demonstrated that adult patients had decreased *S. aureus* relative abundance and increased Shannon diversity 4 weeks after dupilumab treatment, correlating with clinical improvement measured by the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD) tools.[72] Dupilumab, however, did not completely eradicate *S. aureus* as its abundance increased again 32 weeks post-treatment.[72] In a second study ($n = 71$) examining changes in skin microbiota with dupilumab in adults, it was observed that non-lesional skin had lower *S. aureus* abundance compared to lesional skin at study entry. Dupilumab treatment was associated with reduced *S. aureus* abundance to a greater extent in lesional skin as compared to a more modest reduction in non-lesional skin.[73] This suggests that microbiota composition and skin barrier status at baseline may impact response to dupilumab therapy. One study has also reported skin microbiota changes during treatment with tralokinumab, an anti-IL-13 monoclonal antibody. Disease improvement was associated with reduced *S. aureus* abundance and concomitant increase in the relative abundances of CoNS in the lesional skin of adults with moderate-to-severe AD (Phase 3 ECZTRA 1 trial [ClinicalTrials.gov ID NCT03131648]).[74]

Studies investigating skin microbiome with biologics targeting Th2 blockade are still emergent (two studies on dupilumab and one study with tralokinumab), and currently only reported in adults. It is also still unknown if these changes in microbiota composition reflect transient alterations in host skin barrier and immune status, or if these changes are relevant to sustained clinical improvement. Future mechanistic work will be important in determining if skin microbiome changes play an active role in improved clinical response to biologics or reflect an indirect effect due to the normalization of epidermal biology.

8 | THE SKIN MICROBIOME IN FOOD ALLERGY PATHOGENESIS

FA is closely associated with AD, particularly in the early-onset severe phenotype. Murine studies have demonstrated that the pathogenesis of FA may occur through epicutaneous sensitization to food allergens through the disrupted skin barrier in AD (Figure 2). In the murine studies, these mechanistic pathways are postulated to involve activation of dermal antigen-presenting cells upon exposure of inflamed skin to exogenous food allergens, germinal centre IgE+ B-cell expansion and generation of food allergen-specific IgE and other pro-inflammatory cytokines (IL-4, IL-5, thymic stromal lymphopoietin (TSLP) and IL-33).[75,76] A murine model further demonstrated that combined epicutaneous exposure to staphylococcal enterotoxin B (SEB) and OVA enhanced OVA-specific IgE and IgG2 antibody responses compared to OVA exposure alone.[77] Mice which were cutaneously sensitized with SEB and peanut allergen extract had significantly increased peanut-specific Th2 responses compared to mice sensitized with peanut allergen alone.[78] These mouse experiments suggest that SEB may perform an adjunctive role in mediating FA through AD skin.

Recent clinical studies have also highlighted the association of skin microbes with the AD-FA axis. Jones et al. found that children ($n = 718$; aged 0–18 years) with AD who were colonized with *S. aureus*, particularly MRSA, also had a higher risk of FA compared to healthy controls.[79] Infants from the Learning About Peanut Allergy (LEAP) study who were *S. aureus*-colonized during at least one timepoint between 4 and 60 months of age had increased risk of peanut and egg allergy in the first 5 years of life, independent of AD severity.[80]

A cross-sectional metagenomic study ($n = 62$; children aged 4–17 years) of skin microbiota collected from AD patients with FA (ADFA+) showed an increased *S. aureus* relative abundance on their non-lesional skin as compared to healthy subjects. *S. aureus* abundance was also positively correlated with transepidermal water loss in the ADFA+ group but not in AD patients without FA (ADFA−) or healthy groups.[81] A paucity of studies on the differences in overall skin microbiota composition (apart

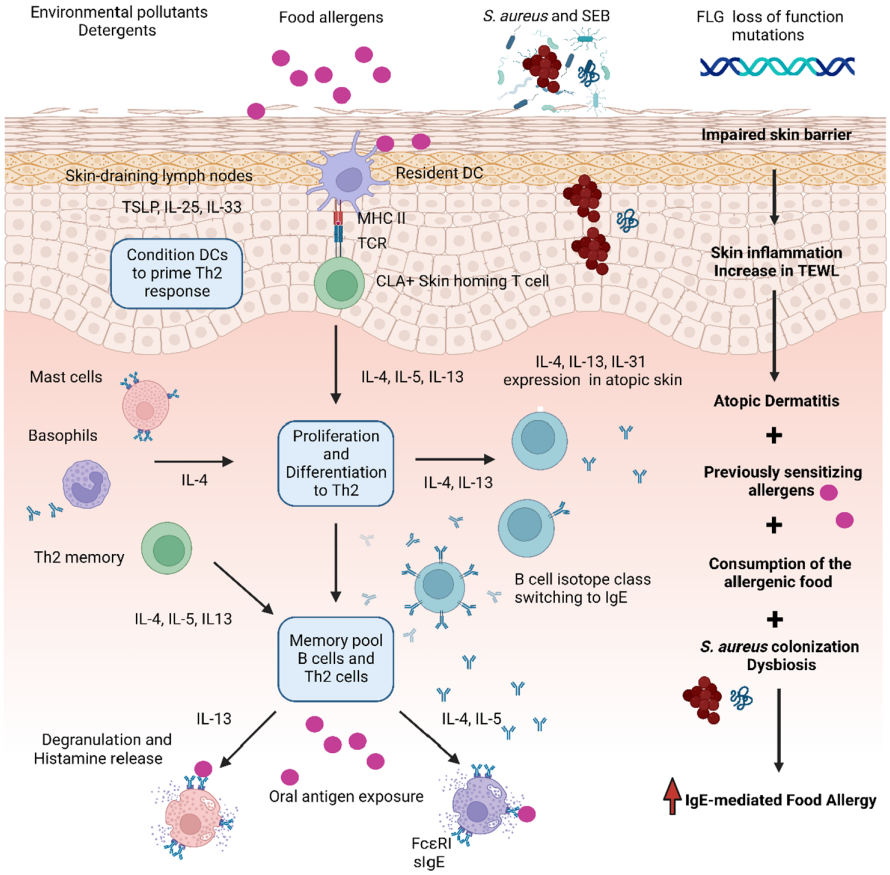

FIGURE 2 Mechanisms of skin barrier dysfunction in atopic dermatitis resulting in food allergy. Environmental pollutants, detergents, microbial dysbiosis and genetics such as *FLG* loss of function mutations can lead to disruptions to the epithelial barrier. Skin barrier impairment leads to skin inflammation resulting in AD. Epicutaneous exposure to food allergens in the context of an impaired barrier may trigger food allergen sensitization through Th2-dependent pathways: specific resident dendritic cell (DC) subsets capture allergens in the skin and transport them to skin-draining lymph nodes where they are presented to the cell surface carbohydrate epitope cutaneous lymphocyte antigen (CLA+) skin-homing T cells. IL-4 and IL-13 cytokines promote B-cell isotype switching to specific IgE (sIgE), and upon differentiating into plasma cells, yield allergen-specific IgE antibodies. The sIgE bind to high-affinity FcεRI receptors on the surface of mast cells and basophils. During the sensitization process, a memory pool of allergen-specific B cells and T helper 2 cells is produced. Upon subsequent oral antigen exposure (consumption of the allergenic food), cross-linking of sIgE on the FcεRI receptors triggers mast cell degranulation, and release of histamine and other inflammatory mediators, culminating in the clinical allergic response. The presence of *S. aureus* enhances pro-inflammatory responses which heightens the risk of FA development. *S. aureus* colonization, such as by methicillin-resistant *S. aureus* (MRSA), and exposure to staphylococcal enterotoxin B (SEB), has been shown to increase the risk of FA independent of AD severity. *S. aureus* abundance was also found to be positively correlated with transepidermal water loss (TEWL) in patients with AD and FA. (Created with BioRender.com).

from *S. aureus* alone), and the temporal evolution of the skin microbiome alongside immune dysregulation, in the development of AD and FA exists.

9 | SKIN-BASED INTERVENTIONS FOR AD AND FA PREVENTION

An increased understanding of the role of the skin barrier and microbiome in AD and FA pathogenesis has sparked interest in developing skin-based interventions for allergy prevention. In the past decade, randomized controlled trials have explored the use of prophylactic skin interventions from early life to prevent the development of AD and FA. A Cochrane individual participant data (IPD) meta-analysis found no benefit of a variety of skin interventions inclusive of emollients, oils and bathing advice overall for AD and FA prevention.[82] Another meta-analysis by Zhong et al. found that prophylactic emollients were effective against AD development in high-risk infants only and in those without an interval between treatment cessation and AD outcome assessment.[83]

A small study in high-risk infants who received emollients ($n = 11$ in the intervention arm and $n = 12$ controls) from birth to age 6 months found greater skin microbiota diversity, lower skin pH and shifts in *Streptococcus* abundance on skin, specifically higher *S. salivarius* and lower *S. mitis* relative abundance, compared to controls.[84] The relative abundance of *S. salivarius* also correlated negatively with

skin pH, suggesting that the lowering of skin pH due to long-term emollient use may either be one of the mechanisms through which changes in skin microbiota composition impact AD development or that these microbial fluctuations merely occur alongside skin barrier changes due to the intervention. Differentiating between these possibilities could not be achieved from this study alone and will require in-depth mechanistic studies such as in murine models to understand the causal interactions between skin emollients, microbiota and the skin barrier.

A randomized controlled trial, the Prevention of Allergy via Cutaneous Intervention (PACI) Study[85,86] found that early enhanced proactive treatment using a low potency topical corticosteroid cream applied to the whole body (lesional and non-lesional skin) of 7–13 week-old infants with AD ($n = 318$) achieved a 25% reduction in hen's egg allergy at the age of 28 weeks when compared with reactive therapy—topical corticosteroid therapy applied only on visible eczema lesions ($n = 322$ infants). This supports the proof-of-concept that early skin barrier repair might protect against the subsequent development of FA through the prevention of epicutaneous sensitization. However, this study did not specifically examine the mechanistic pathways through which FA prevention was achieved, nor the role of the skin microbiome in FA prevention.

10 | SKIN MICROBIOME-BASED APPROACHES FOR AD TREATMENT

In contrast to broad-spectrum antibiotic therapies, repurposing commensal and symbiotic microbes for therapeutic strategies could allow more targeted antimicrobial effects against pathogenic microbes without unintended collateral impact on the rest of the healthy microbiota. Microbiome studies have now investigated numerous microbial mechanisms by which AD skin could benefit from a microbial-driven anti-inflammatory outcome. The earliest studies utilized a b*acterial lysate of Vitreoscilla filiformis as AD therapeutics*. The proposed mechanism was via host antimicrobial peptides and anti-inflammatory effects.

A subsequent MRSA skin infection murine study demonstrated that CoNS species can play an important role in activating other microbes and can also interact with the epidermis to maintain homeostasis and interact or compete with *S. aureus*.[87] *S. epidermidis* is an important CoNS that has been shown to reduce skin inflammation by regulating TLR pathways and can produce sphingomyelinase to aid in the production of ceramides to maintain the skin barrier in mouse and in vitro models.[88,89] These functions suggest an important role *S. epidermidis* has on the skin and the potential that could be harnessed for AD.

TABLE 1 Key research questions and future research directions.

Key research questions	Future research directions
Changes in skin microbiota composition	
• Do shifts in skin microbiota composition impact disease pathogenesis or do they merely reflect underlying disease processes?	• Mechanistic studies designed to assess the effect of changing skin microbe abundances on disease pathogenesis • Intervention studies to understand the role of microbes in disease pathogenesis
• How do skin microbiota interact with one another, and with the host to influence disease pathogenesis?	• Functional analysis of the contribution of microbes e.g. bacteria, viruses, fungi and mites colonizing skin to skin disease • Use of deep sequencing methods integrated with culture methods and measures of skin barrier function to determine the role of microbes in disease pathogenesis • Standardization of protocols across skin phenotyping studies to allow for comparison of data • Murine models investigating combinations of microbes, and deep endophenotyping of host responses
• Do skin microbiota alterations in early life impact AD and FA onset in later childhood • If so, what are the mechanisms through which this might occur?	• Larger longitudinal studies with long-term follow-up, robust early-life skin barrier measures and objective allergic outcomes • Mechanistic studies to validate the impact of changes in microbe composition on disease onset
Skin microbe-based therapeutic approaches	
• Does therapeutic manipulation of skin microbiota prevent AD or FA or reduce disease severity? • If so, what is the window of opportunity for such interventions?	• Randomized controlled trials of early-life skin microbiota manipulation with long-term follow-up for allergic disease onset • Detailed collection of skin barrier markers at serial time points in early life
• Which patient groups would benefit from biotherapeutic interventions?	• Intervention studies to include different disease phenotypes e.g. infected AD, positive colonization with target microbe, etc
• Would disruption of pathogenic skin microbiota transmission between close contacts improve outcomes?	• Randomized controlled trials of microbe eradication techniques involving close contact with index patients

TABLE 2 Skin microbiome clinical trials in children.

NCT Number	Study title	Subjects
Trials monitoring skin microbiota changes in response to treatment		
NCT01597817	Efficacy and safety of a biofunctional textile in the management of atopic dermatitis	Subjects above 12 years of age with atopic dermatitis
NCT01631617	Effects of treatments on atopic dermatitis	Cohort 3: subjects 2–50 years of age with atopic dermatitis and symptoms of active bacterial infection
NCT03376243	EARLYEMOLLIENT – Feasibility of early emollient use in children with atopic eczema	50 high-risk neonates from Days 1–21 of life
NCT03673059	Clinical trial to assess the effects of topical lotions on changes in the skin microbiome and associations with itch	Subjects 16–50 years of age with mild to moderate eczema with recent flare
NCT04800185	Characterizing skin microbiome change in atopic dermatitis	Patients 2 years and above with atopic dermatitis
NCT05523986	Vitamin D treatment effect for atopic dermatitis in children	Children 1–18 years with moderate to severe AD
NCT03614221	Comparison of Lindioil (Indigo Naturalis Oil Extract) Ointment to Protopic® Ointment 0.1% in treating atopic dermatitis	Patients 16–65 years with atopic dermatitis
NCT05688735	Assessment of the effect of coconut and sunflower seed oil-derived isosorbide diesters and colloidal oatmeal	Children 2–17 years with active atopic dermatitis
Trials on microbiota-based interventions		
NCT04265716	Topical *L. reuteri* in children with atopic dermatitis	Children 1–18 years of age with atopic dermatitis
NCT04771910	Study of the skin microbiome and the potential of a topical probiotic cream for atopic dermatitis	Patients with atopic dermatitis
NCT03928431	Restoration of microbiota in neonates	Infants of healthy mothers with uncomplicated pregnancies at term

Abbreviations: ADSI, Atopic Dermatitis Severity Index; EASI, Eczema Area Severity Index; POEM, patient oriented eczema measure; SCORAD, SCORing AD severity; TEWL, transepidermal water loss.

Interventions	Outcome measures
Randomized blinded controlled trial Intervention: chitosan coated textile (cotton long-sleeved shirts and pants) Comparator: chitosan-free cotton long-sleeved t-shirts and pants	• SCORAD • Quality of Life • Eczema symptoms • Eczema treatment • Immunological markers • Skin microbiota (*S. aureus*) • Genetic mutations
Randomized blinded controlled trial Intervention: Cephalexin with dilute bleach bath Comparator: Cephalexin with placebo bath	• Difference in Shannon Diversity Indices (SDI) from baseline to Day 14
Pragmatic, parallel-group, assessor-blind randomised open-label prospective study Intervention: LIPIKAR BAUME AP+ emollient Comparator: Structured parent education	• Willingness to participate • Cumulative incidence of eczema • TEWL • Microbiome diversity over time
Randomized blinded controlled trial Intervention: Cosmetic moisturizer regimen DRUG: OTC eczema moisturizer	• Microbiome composition • pH changes • TEWL • Skin hydration • EASI score • ADSI score
Open-label trial DRUG: Crisaborole 2% topical ointment Comparator: None	• Skin microbiome before, during and after treatment with crisaborole 2% ointment
Randomized controlled trial Intervention: Vitamin D (2000 IU/day) for 6 months Comparator: Placebo	• Vitamin D levels • Genotyping • Nasal, skin and anal microbiota composition • Total and antigen-specific IgE • EASI • POEM
Randomized cross-over trial Intervention: Lindioil ointment Comparator: Protopic 0.1% ointment	• EASI-50, EASI-75, EASI-90 • Investigator's Global Assessment (IGA) • Body surface area of involvement • Length of relapse-free days after treatment cessation • Pruritus symptoms • Quality of life • Skin microbiome changes
Randomized blinded controlled trial Intervention: Isosorbide Diester (0.1% colloidal oatmeal) + topical hydrocortisone 2.5% ointment Comparator: Placebo vehicle (with 0.1% colloidal oatmeal) + topical hydrocortisone 2.5% ointment	• EASI • Itch symptoms • Topical steroid use • TEWL • Skin hydration • Change in *S. aureus* abundance on skin
Intervention: Topical probiotic *L. reuteri* Comparator: standard of care + placebo	• Improvement in skin appearance • SCORAD at 16 weeks
Randomized controlled trial Intervention: Topical cream with live probiotic (*Lactobacillus*) Comparator: placebo cream	• Skin microbiome composition • EASI • Skin itch symptoms
Randomized controlled trial Intervention: swab from maternal vagina + faecal swab on Caesarean-born infants' skin Comparator: Clean saline-soaked gauze	• IgE-associated allergic disease at 2 years of age • Immunological markers • Microbial composition between groups

However, the use of *S. epidermidis* without attenuation would be complex, and potentially controversial, due to its dual roles in protection from pathogens and ability to stimulate inflammation or cause systemic infections in certain situations.[90] Additionally, there have also been recent potential biotherapeutic approaches using the non-bacterial components of the microbiome such as bacteriophages to target *S. aureus* but not *S. epidermidis*.[91]

Clinical studies have further validated the above observations from murine models. In a randomized, double-blind, vehicle-controlled trial, mild AD subjects ($n = 75$ aged 6–70 years) who received topical applications of *V. filiformis* experienced improvements in SCORAD and pruritus scores, as well as the downward trend of *S. aureus* skin burden and drop-outs related to lack of efficacy.[92] Transplantation of CoNS commensal microbe *S. hominis* from healthy patients onto AD skin has also been investigated. CoNS strains from healthy volunteers produced potent AMPs that reduced *S. aureus* on the skin of 5 adult AD subjects.[36] A subsequent follow-up phase 1 clinical trial using the *S. hominis* A9 (ShA9) strain in 54 adult AD patients demonstrated safety; however, eczema severity was not significantly different when examined among all treated participants.[93] A post-hoc analysis showed that a subgroup of patients who were colonized by *S. aureus* strains which were sensitive to killing by ShA9 showed significant clinical improvement compared with vehicle.[93] A phase 2 clinical trial [ClinicalTrials.gov ID: NCT05177328] is ongoing to further investigate this approach.

Another bacteriotherapy approach used *Roseomonas mucosa* a skin commensal harvested from healthy donors, as topical therapy for AD. An open-label phase I/II trial with 10 adult and 5 pediatric subjects who received skin treatment with *R. mucosa* demonstrated improved disease severity, reduced topical steroid requirements and decreased *S. aureus* burden.[94] However, the phase II placebo-controlled clinical trial [ClinicalTrials.gov ID: NCT04936113] which combined three strains of *R. mucosa* for a live therapeutic product (FB-401) in AD patients was terminated because it failed to demonstrate any significant differences in patients for achieving the primary outcome of EASI-50 (the proportion of subjects with a minimum of 50% improvement in AD disease severity as measured by the Eczema Area and Severity Index (EASI) score).

Bacteriophage endolysin-based therapies have also been developed as AD therapeutics. Staphefekt SA.100 is a commercialized topically administered recombinant phage endolysin which was able to reduce AD symptoms and skin inflammation in early-phase studies. However, in a follow-on double-blinded, vehicle-controlled randomized superiority trial in adults with non-clinically infected moderate-to-severe AD [ClinicalTrials.gov ID: NCT02840955], the endolysin intervention failed to demonstrate superiority over placebo in topical steroid usage, clinical efficacy, quality of life or *S. aureus* burden.[95] However, this trial excluded patients with clinically infected AD and only half of the cohort were colonized with *S. aureus* prior to enrolment.

Due to the individuality of skin microbiomes at the strain level in both healthy individuals and AD patients, bacteriotherapy may be effective only in heavily colonized or clinically infected AD, but may be less effective in other circumstances. It is therefore likely that these microbial therapeutic approaches will require careful patient selection to identify specific subgroups who will benefit from such interventions, and optimization of therapeutic design to achieve sustained clinical responses.[93,95]

11 | CONCLUSION

Numerous studies have now reported that the composition of the skin microbiome is closely associated with AD flares, severity and response to various treatment modalities. However, skin microbiota is not the sole factor in AD where genetics, immunology and environmental influences also play important roles.

Several gaps in the existing literature remain to be filled and it is hoped that future studies will address these (Table 1). Many studies currently demonstrate differences in skin microbiota composition in cases and controls at a single time point, which limits our ability to make conclusions about causality and temporal progression; or focus on bacterial species alone but do not explore other microbes such as viruses and fungi or their interactions with bacteria and the host. There is also a lack of mechanistic understanding of functional units in the skin microbiome and whether differences in microbial abundance impact clinical disease or are mere bystanders reflecting fluctuations in clinical disease.

Future research should focus on several broad areas: (1) a mechanistic understanding of whether skin microbial shifts modulate or merely reflect AD and FA pathogenesis, treatment response or disease prevention; (2) functional analysis of all skin microbes including bacteria, viruses, fungi and mites in deep metagenomic studies integrated with culture methods and skin barrier function analysis to understand their potential interactions with each other to impact disease phenotypes or progression; (3) longitudinal studies to identify the window of opportunity for intervention, if any; (4) evaluating the efficacy, sustainability and patient selection for microbe-based biotherapeutics in disease treatment and prevention. (Table 1).

Several interventional trials that are underway in children with AD focus mainly on monitoring skin microbiota changes in response to treatment and microbiota-based interventions, such as probiotics in topical creams and vaginal microbiota seeding (Table 2). However, apart from the latter study, the majority of these trials plan only to document changes in skin microbiota composition as secondary aims. There is a clear need for more robust studies to fill the gaps described above, and to move the field away from merely descriptive studies to understanding the mechanistic role and functions of skin microbiota in disease pathogenesis and treatment, and to evaluate the potential to harness them for targeted biotherapeutic interventions or as validated biomarkers of disease.

AUTHOR CONTRIBUTIONS

Elizabeth HW Tham contributed to conceptualization, project administration, writing the original draft, reviewing and editing the manuscript. Carmen Riggioni and Minghao Chia contributed to visualization, writing the original draft, reviewing and editing the manuscript. Niranjan Nagarajan and John EA Common contributed to writing the original draft, reviewing and editing the manuscript. Heidi H Kong contributed to reviewing, revising and editing the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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