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CME Review

Skin as the target for allergy prevention and treatment

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Key Messages

- Disruption of the skin barrier is associated with development of atopic sensitization.
- Atopic dermatitis is associated with immune dysregulation, which can both cause epithelial disruption and be a result of epithelial disruption.
- Both the gut and skin microbiome have been shown to have effects on skin epithelial barrier function.
- Barrier-based approaches are valuable for disease prevention; however, Th2 cytokine targeted immune-based treatments and immune abnormalities should be addressed in order to improve and resolve active atopic dermatitis and prevent food allergy development.
- Newer treatments for atopic dermatitis that are being explored include pro and prebiotics, filaggrin replacement therapies, and skin-targeted gene therapy.

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ABSTRACT

The fact that genetic and environmental factors could trigger disruption of the epithelial barrier and subsequently initiate a T_H2 inflammatory cascade conversely proposes that protecting the same barrier and promoting adequate interactions with other organs, such as the gut, may be crucial for lowering the risk and preventing atopic diseases, particularly, food allergies. In this review, we provide an overview of structural characteristics that support the epithelial barrier hypothesis in patients with atopic dermatitis, including the most relevant filaggrin gene mutations, the recent discovery of the role of the transient receptor potential vanilloid 1, and the role involvement of the microbiome in healthy and damaged skin. We present experimental and human studies that support the mechanisms of allergen penetration, particularly the dual allergen exposure and the outside-in, inside-out, and outside-inside-outside hypotheses. We discuss classic skin-targeted therapies for food allergy prevention, including moisturizers, steroids, and topical calcineurin inhibitors, along with pioneering trials proposed to change their current use (Prevention of Allergy via Cutaneous Intervention and Stopping Eczema and ALlergy). We provide an overview of the novel therapies that enhance the skin barrier, such as probiotics and prebiotics topical application, read-through drugs, direct and indirect FLG replacement, and interleukin and janus kinases inhibitors. Last, we

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discuss the newer strategies for preventing and treating food allergies in the form of epicutaneous immunotherapy and the experimental use of single-dose of adeno-associated virus vector gene immunotherapy.

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At the conclusion of this activity, participants should be able to:

- Specify the importance of the epithelial barrier in the development of food allergies.
- Categorize classic and novel skin-targeted therapies for food allergy prevention.

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Introduction

The IgE-mediated allergic diseases (also called atopic diseases) such as asthma, atopic dermatitis (AD), allergic rhinitis (AR), and food allergy (FA) have been increasing in the last few decades.[1] Although their prevalence varies between studies because of differences in methodology and demographics, the prevalence of different atopic conditions in the United States is estimated to be approximately 10% to 30% for AR, 4% for asthma, 10% to 20% for AD, and 11% for FA.[2-4] These diseases have been found to be highly heritable. In this sense, it is estimated that between 35% and 95% of patients are diagnosed with asthma, 33% to 91% of those with AR, 71% to 84% of those with AD, and 81% of those with FA have a parent who shares the same diagnosis.[5,6] Although the high heritability of these diseases indicates the critical role of genetics, genetics alone cannot fully explain the rapid growth in their prevalence. Environmental factors such as air pollution and climate change are thought to play an important role in the increasing prevalence.[5,7] One systematic review and meta-analysis of 55 papers found a significant association between air pollutants and increased risk of allergic diseases.[7]

Atopic diseases seem to have natural disease progression with AD being the first to manifest, followed by FA, AR, or allergic asthma, suggesting a common underlying mechanism and perhaps different manifestations of the same disease. This natural progression has been termed the atopic march.[8] It is currently hypothesized that disruption of the epithelial barrier is the first step in initiating an inflammatory allergic pathway.[9] This has been termed the epithelial barrier hypothesis (Fig 1). Both genetic and environmental factors have been found to mediate epithelial barrier dysfunction.

There is growing evidence that environmental peanut exposure through the skin can result in peanut sensitization and allergy.[10] A study in highly atopic children with an impaired epidermal barrier found an exposure-response relationship between peanut protein levels in household dust and peanut sensitization and likely allergy.[11] Other foods, such as cow's milk, egg, walnut, and fish, have also been found in dust.[11] In this review, we expand topics to understand the importance of skin barrier function in the development of FA and how to target the skin barrier for FA prevention and treatment.

Skin Barrier Function and Dysfunction in Atopy

In addition to providing protection from external threats, the skin helps the internal milieu by protecting the body from water loss and maintaining homeostasis. The human epidermis is composed of 5 layers, which are formed through keratinocyte differentiation to create the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (SC).[12] The SC is the outermost layer and contributes the most to skin barrier function, as important proteins and lipids in the SC provide structural integrity. This cornified layer is composed of filaggrin and other epidermal differentiation complex (EDC) genes, including loricrin and involucrin. Tight junction proteins in the stratum granulosum provide additional barrier protection and contribute to water retention. Epidermal ceramides, including acylceramides, are also important for skin barrier function. Together, the components of the SC are necessary to maintain skin integrity, pH, and moisturization.[12,13]

Transepidermal water loss (TEWL) quantifies the amount of water that moves from the dermis and epidermis through the SC to the skin surface. In healthy skin, the SC functions as an efficient barrier minimizing water loss. However, in diseases such as AD, this barrier is damaged, resulting in significantly larger water loss, which serves as a measure of epithelial barrier integrity (Fig 2).[14] Consequently, TEWL is frequently used to evaluate the severity of AD and the response to treatment.[10] It is also notable that TEWL, particularly after skin tape stripping, can differentiate between diverse AD endotypes with and without peanut allergy (PA).[15]

Recent studies have revealed that distinct skin endotypes are found in individuals with AD but without FA, AD, and FA and FA without AD.[16] The skin barrier profile in these groups is distinct in the protein and ceramide expression and *Staphylococcus aureus* abundance. This reveals the important role of the skin barrier in atopy and that these endotypes have distinct findings in the SC epidermal layer. Moreover, FLG loss-of-function mutations have been well studied and are the strongest genetic risk factor for AD. Other defects, such as tight junction polymorphisms in claudin-1 and Notch deficiency, have also been described to interfere with keratinocyte differentiation.[13] Disruption of keratinocyte differentiation allows for allergens and irritants to enter through the damaged skin, leading to an increase in proinflammatory cytokine expression.[13]

Environmental Irritants

Skin irritants including detergents and pollutants lead to reduced FLG expression and skin barrier damage.[12,13] Surfactants affect tight junctions potentially increasing risk of allergic reactions.[17] Some

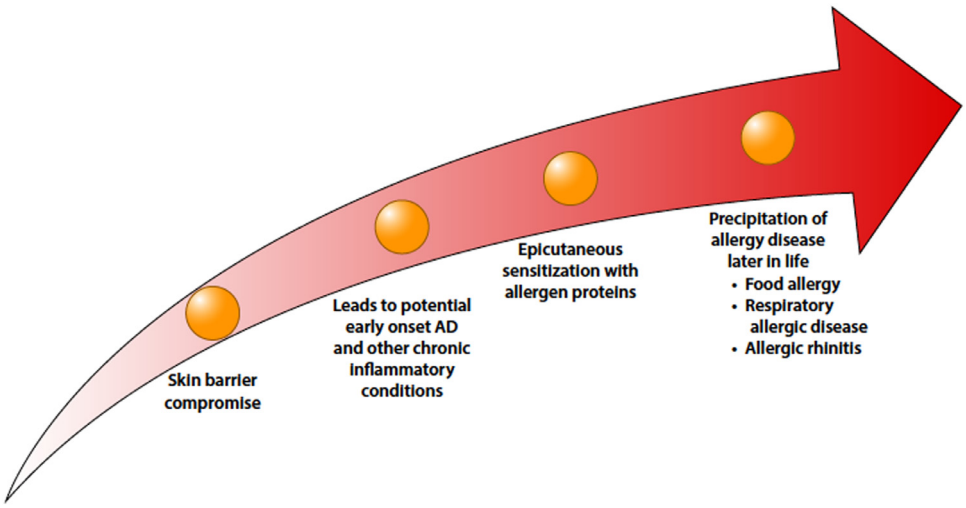

Figure 1. The sequence of events after skin barrier compromise early in life. AD, atopic dermatitis.

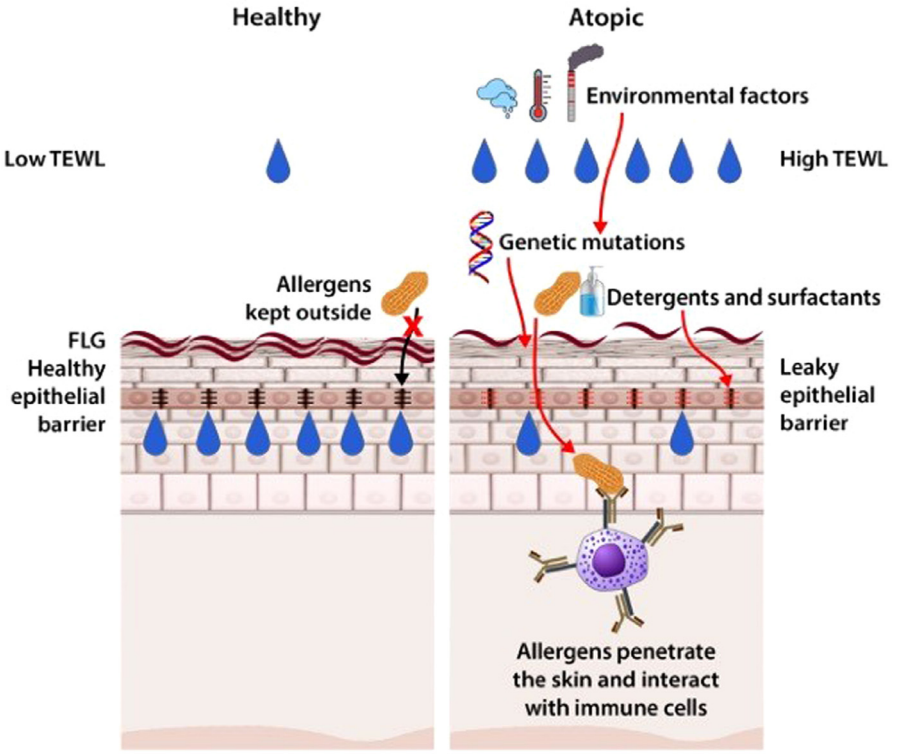

Figure 2. TEWL findings and factors contributing to epithelial barrier dysfunction in AD against healthy skin. AD, atopic dermatitis; TEWL, transepidermal water loss.

compounds found frequently in cleaning products, such as sodium dodecyl sulfate and sodium dodecylbenzene sulfonate, damage the epithelium even at dilutions of 1:100,000.[17] Concurrently, pollution inhibits EDC genes.[18] In addition, environmental factors are critical in early childhood, as babies begin their exposure to the world. Season, month, and time of birth can indirectly measure changes experienced during pregnancy and early infancy, such as temperature, humidity, sun exposure, and outdoor physical activity[19]; for example, in children born during the fall and winter, there is a higher incidence of AD.[20] Furthermore, low humidity triggers FLG proteolysis, increasing the skin barrier disfunction.[21]

More recently, the role of transient receptor potential vanilloid 1 has been studied as a temperature-sensing ion channel expressed in epidermal keratinocytes. Low temperature causes skin barrier dysfunction by inhibiting EDC genes and increasing proinflammatory cytokines through transient receptor potential vanilloid 1, which may be a contributing factor to worsening AD during winter.[22] Thus, there are many components of the skin barrier that contribute to its important defense mechanisms, and genetic and environmental factors can lead to impaired function.

Mechanisms of Allergen Penetration

The Dual Allergen Exposure Hypothesis

The dual allergen exposure hypothesis proposes that the route of exposure to food allergens determines whether an individual develops tolerance or sensitization to the allergen. Early oral exposure to food allergens is thought to induce tolerance, whereas exposure to food and potentially respiratory allergens through the skin can lead to sensitization and the development of food and respiratory allergies (Fig 3).[23-26]

The application of peanut oil to inflamed skin during infancy is a risk factor for the development of PA.[27] There is also a dose-response relationship in infants with atopy between environmental peanut exposure (measured by household peanut consumption) and the development of PA, but this relationship no longer existed in infants who ate peanut in their first year.[28]

The Outside-In, Inside-Out, and Outside-Inside-Outside Hypothesis

The AD is characterized by both epidermal barrier dysfunction and immune dysregulation, with skewing toward a T_H2 profile. However, whether the epidermal barrier abnormality leads to the immunologic abnormalities (the outside-in hypothesis) or the immunologic mechanisms exacerbate barrier integrity (the inside-out hypothesis) is unclear. Indeed, both mechanisms may have a role to play. Both an impaired skin barrier and immune dysregulation (T_H2 deviation) begin in early infancy. Studies have revealed that there is overexpression of interleukin (IL)-4 and IL-13 in AD skin. In the presence of these cytokines, keratinocytes exhibit reduced FLG gene expression. The interaction between these 2 theories may explain the mechanism for the outside-inside-outside hypothesis.[29]

Role of Skin Barrier Dysfunction in Allergy Development

The integrity of the SC is maintained by a careful balance of lipids including ceramide, free fatty acids, and cholesterol.[30,31] Atopic skin is associated with alterations in several SC lipids including altered lipid organization, a decrease in total lipids, and altered ratios of ceramides, free fatty acids, and cholesterol.[32-34] In atopic skin, lipids are less densely organized, which could be due to the shift toward short- as opposed to long-chain ceramides.[34] Similar findings have also been found with free fatty acids, with a significant decrease in long-chain fatty acid (≥24 carbon atoms) and an increase in the short-chain fatty acid, such as C16 (palmitic acid) and C18 (octadecanoic acid) in atopic skin.[35]

In addition to the lipid profile of the skin, the role of filaggrin and its breakdown product such as natural moisturizing factor are critical for maintaining skin barrier function. Null mutations

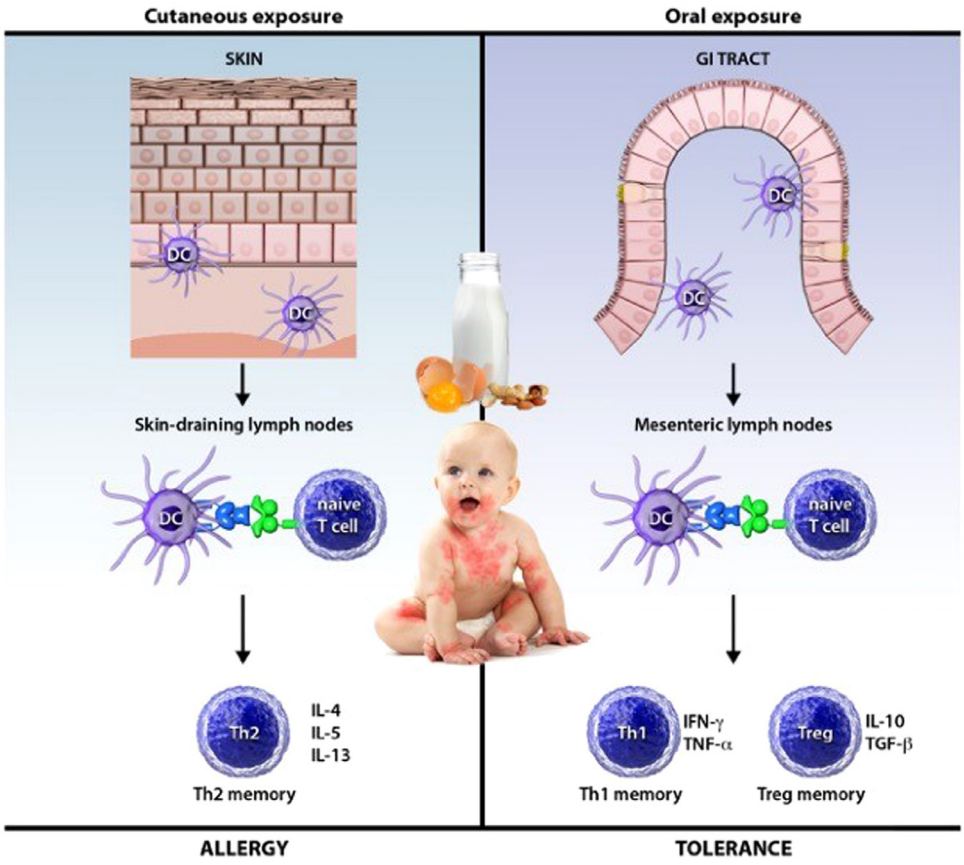

Figure 3. Dual-allergen exposure: increasing evidence suggests that early life allergen exposure through the skin causes T cell deviation toward a T_H2 allergenic type and subsequent food allergy, whereas early oral exposure causes T cell deviation toward tolerogenic T_H1 and Treg subtypes (dual allergen exposure hypothesis). Adapted from: Brough HA, Nadeau KC, Sindher SB, Alkotob SS, Chan S, Bahnson HT, et al. Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented? Allergy. 2020;75(9):2185-205. GI, gastrointestinal.

in the FLG gene were first identified as a risk factor for AD in an Irish cohort, in which they found the FLG polymorphisms FLG R501X and 2282del4.[32] FLG null mutations still hold the strongest genetic predisposition for skin barrier defects. FLG is translated as the precursor proprotein profilaggrin, which can be broken down to form filaggrin monomers. Filaggrin monomers induce the aggregation of skin keratin filaments resulting in the formation of large macrofibrils,[36] which play key roles in enhancing the strength and flexibility of the SC.[37] Furthermore, these filaggrin monomers can undergo further proteolysis leading to the generation of trans-urocanic acid (UCA) and pyrrolidone carboxylic acid, which are components of natural moisturizing factor.[38] Therefore, filaggrin provides both mechanical strength and hydration to the SC, and disruption of this pathway results in impaired hydration, increased acidification, and abnormal lipid content, distribution, and organization in the skin.

The FLG genetic variants were found to have a highly significant association with asthma occurring in the context of AD.[32] The disrupted epithelial barrier facilitates the entry of environmental substances through the skin promoting a T_H2 inflammatory cascade.[39] Although there is an increased risk of FA in children with AD, a significant number of children who develop FAs do not have AD, but may only have impaired skin barrier function.[40] Furthermore, FLG loss-of-function mutations were found to have a significant association with PA even after controlling for co-existing AD.[41] This was not replicated in children without skin barrier dysfunction, suggesting that the skin barrier plays a key role. Household peanut exposure has been associated with peanut sensitization and PA, if the child had FLG null mutation[42] and AD.[11,42]

Role of the Skin Microbiome in Allergy Prevention

In healthy skin, there is a stringent selection process governing the microbiome. This is secondary to the interaction of environmental exposure, host factors, and metabolism products. The characteristic dysbiosis present in AD implies an immune system imbalance and skin barrier malfunction.[15] In this sense, environmental factors and genetics could disturb these interactions and trigger harmful bacteria overgrowth.[15]

S aureus, in particular, is widespread in subjects with AD, in which it tends to be more virulent through varied mechanisms; a compromised barrier is more prone to colonization because of the redistribution of fibronectin in the SC.[15,43] Furthermore, patients with FLG mutations have higher skin pH due to lower levels of FLG-degradation products and have an enhanced tendency to generate biofilms, all contributing to successful colonization and avoidance of the immune system.[43] Overall, *S aureus* proliferation has been linked with AD severity, progression, and persistence.[43,44]

Recent research has shed light on the intricate relationship between *S aureus* overgrowth in AD and the development of FAs.[10,45-47] Its presence in the skin at any point hinders the natural occurrence of tolerance to hen's egg and interrupts the process of developing tolerance to peanut.[44] Moreover, it has been associated with higher levels of IgE in cow's milk, hen's egg, and peanut independent of the AD severity.[44] The virulence of *S aureus* through the production of Staphylococcus enterotoxin B is also recognized as an amplifier of allergic responses to food allergens.[48,49]

Malassezia spp is an abundant part of the healthy skin microbiome. Despite that, the overgrowth of specific species such as *Malassezia furfur, Malassezia sympodialis*, and *Malassezia globosa* has been

related to AD and its severity. The distribution of skin lesions in the head and neck suggests an association with these microrganisms.[50] Furthermore, the reactivity to pathogenic *Malassezia* in patients with AD can be identified through specific IgE levels, skin prick, and patch tests. Selander et al[48] recognized that *Malassezia sympodialis* induces cysteinyl leukotrienes in IgE-sensitized bone marrow-derived cells, secondarily activating mast cells and preserving inflammation in patients with AD.

The previous evidence emphasizes that skin dysbiosis plays a fundamental role in AD severity and progression, potentiating allergic responses and magnifying the risk of food sensitization and FA persistence (Fig 4). Current evidence also supports a role for the gut microbiome in AD; however, because of the co-evolution with humans, commensal gut bacteria play a key role in preventing several chronic inflammatory diseases, including AD, through interactions with the epithelial barrier and mucosal immune system that may have systemic outcomes.

Although viral infections in the skin of patients with AD may become disseminated and thereafter worsen AD control, there are no data on whether this further increases predisposition toward atopy.

Gut Microbiome and Skin Barrier Dysfunction

Numerous studies have identified microbial differences in patients with AD when compared with healthy individuals, and infants with decreased gut microbial diversity are particularly susceptible to the development of AD.[51-56] Cohort studies have identified several key bacteria differentially expressed in the gut in persons with AD, including *Bifidobacterium* (in infants) and *Clostridium sp* (in adults), that metabolize indigestible complex polysaccharides into many essential nutrients, including the short-chain fatty acids, butyrate and propionate, and the neurotransmitters, Gamma-aminobutyric acid (GABA) and acetylcholine. Butyrate enhances epithelial barrier function thereby decreasing the permeability of the intestinal barrier.[57,58] In the relative absence of butyrate in the gut, the epithelial barrier loses integrity allowing for the penetration of undigested food, toxins, and certain microbes, termed "pathobionts," into the systemic circulation. A strong T_H2 response is in turn initiated in the skin causing significant tissue damage.[59] Furthermore, butyrate is essential for the proper development of the mucosal immune system inducing development of regulatory T cells.[57] Finally, GABA, the most common inhibitory neurotransmitter, plays an essential role in itch restriction, whereas acetylcholine plays a critical role in both the development and maintenance of the skin epithelium.[59]

Although the role of the gut microbiome in AD is compelling, whether manipulation of intestinal microbes with probiotics will affect AD remains less clear. Although conditioned and supported by very low-quality evidence, the World Allergy Organization has determined that there is a likely net benefit from using *Lactobacillus rhamnosus GG* supplementation during pregnancy to prevent high-risk infants from developing AD.[60] Several studies evaluating the treatment of AD with probiotics have failed to find consistent benefit; however, this lack of efficacy is likely due to the fact that the bacteria used in commercially available probiotics more closely resemble that in infants' guts.[61] Butyrate-producing, anaerobic bacteria that more closely resemble that which is found in adolescents and adults have yet to be encapsulated in a form that resists oxygen degradation. Although development of effective probiotics is ongoing, immune-regulating prebiotics, such as natural fibers, and post-biotic therapies, such as GABA and butyrate, may soon provide a steroid-sparing alternative treatment for AD.[61]

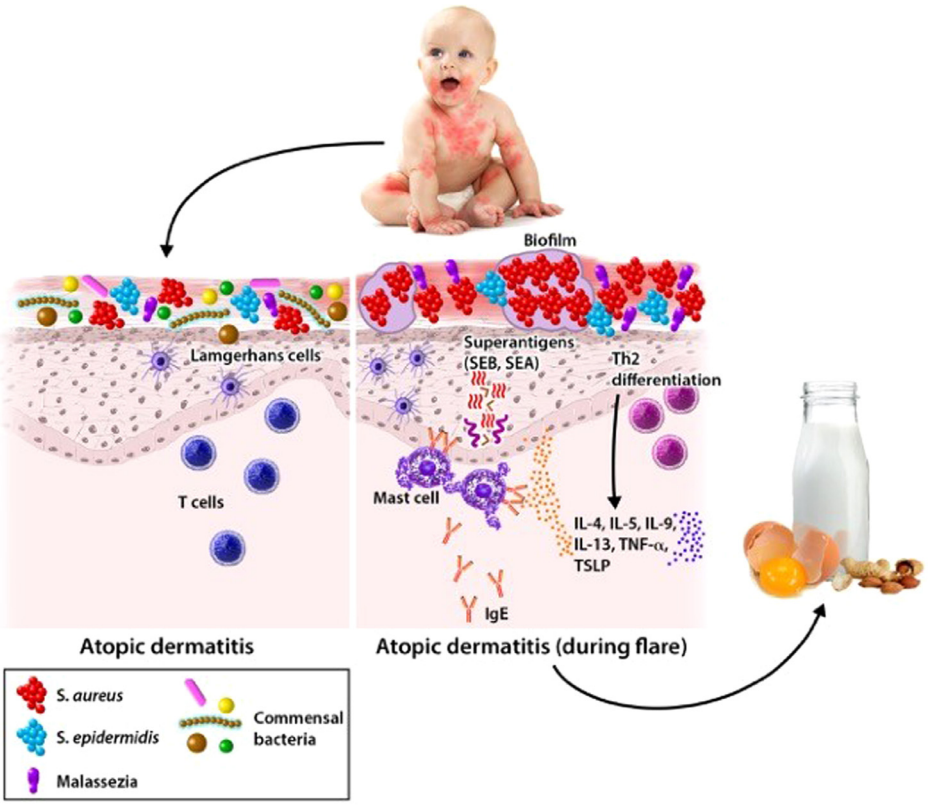

Figure 4. Microbiome dysbiosis in AD. Flares are characterized by less microbial diversity, increased harmful bacteria (*Staphylococcus aureus*) and fungi (*Malassezia*), and further wall disruption. *S aureus* superantigens activate IgE-mediated mast cells leading to T_H2 responses. The sustained colonization by *S aureus* has been related to increased production of serum-specific IgE to cow's milk, egg, and peanut. AD, atopic dermatitis.

Skin-Targeted Therapies for Atopic Dermatitis and Food Allergy Prevention

Strengthening Skin Barrier Function: Moisturizing Agents

The type of topical therapy that provides the best skin barrier protection has been evaluated in several studies including non-lipid emollients, emollients containing at least 1 ceramide, and a combination of emollients and topical steroids.[10] Petrolatum-based emollients are currently considered the gold standard ointment-based emollient for the management of AD.[62] Nevertheless, in some patients, petrolatum-based emollients can exacerbate AD. It is thought that trilipid creams, which mimic the skin's natural pH and lipid composition (3:1:1 ratio of ceramides, cholesterol, and free fatty acids), may be most effective in maintaining skin integrity.[63,64] However, these are not available in many countries. Trilipid emollients have been reported to be more effective than paraffin-based emollients in reducing TEWL and total and specific IgE levels when compared with petrolatum-based emollients.[65]

Emollients for the Prevention of Atopic Dermatitis

Several studies have evaluated emollients as a preventive strategy against AD. In a Cochrane review evaluating the effect of skin care interventions (including emollient application and bathing practices) on the prevention of AD and FA in infants,[66] the authors concluded that "This review found that skin care interventions such as emollients probably do not influence the development or time to onset of eczema in healthy term infants by age 1 to 2 years and probably increase the risk of skin infection."[66] Factors such as frequent infant bathing before the onset of AD and bath emollients (baths with oil- or emulsifier-based additive) have been found to increase the risk of AD.[67,68]

Conversely, a systematic review and meta-analysis of only preventative emollient therapy (not bathing practices) found that the prophylactic application of emollients initiated in early infancy may prevent AD, especially in high-risk populations and when used continuously up until the point of AD assessment.[69] Since the release of these meta-analyses, the STOP-AD (Short-term Topical Application to Prevent Atopic Dermatitis) trial has found a significant reduction in AD cumulative incidence by 1 year of age in high-risk infants who had a ceramide-based emollient applied in the first 2 months of life and then discontinued.[70]

Emollients for the Prevention of Food Allergy

There are contradictory results regarding the use of preventative emollient therapy to prevent FA. The Prevention of Eczema By a Barrier Lipid Equilibrium Strategy pilot study revealed a reduction in investigator-observed AD and food sensitization (by skin prick test) at 12 months with a trilipid emollient therapy in the per-protocol group.[71] However, several studies have found no significant reduction of the incidence of AD, such as the Barrier Enhancement for Eczema Prevention and the study Preventing AD and ALLergies in Children studies. The Barrier Enhancement for Eczema Prevention study also found a higher rate of skin infections in the intervention group and higher trend toward increased FA.[72] Furthermore, in a retrospective review of skin emollient applications in participants of the Enquiring About Tolerance study, a dose-dependent association was found between frequency of application of emollients (predominantly olive oil) and the development of food sensitization allergy.[64] It should be noted that in a study evaluating emollient for the treatment of AD, 65% of these contained contact allergens.[73]

Further studies are needed to reach definite conclusions. The Stopping Eczema and ALlergy study (NCT03742414[74]), among others, is a randomized, controlled, parallel-design, open-label phase 2 clinical study that compares the effect of early proactive skin care with petrolatum-based emollients vs trilipid-based emollients, against standard-of-care AD therapy, to reduce occurrence and severity of AD in children and prevent FA at 3 years of age.

Proactive Steroid Use and Topical Immunomodulators

Barrier-based approaches are valuable for disease prevention; however, immune-based treatments targeting T_H2 cytokines and immune abnormalities probably need to also be addressed to improve and resolve active AD and prevent FA.[62,75] Proactive topical anti-inflammatory therapy is defined as a combination of long-term anti-inflammatory treatment applied initially daily to achieve control and then usually down-dose to 2 to 3 times per week for 16 weeks to maintain control in previously affected areas of the skin. This therapy can be done using topical corticosteroids and/or with topical calcineurin inhibitors (TCIs) in combination with an emollient (liberal use) with scheduled appointments to review AD control and monitor for any adverse effects[75-78] (Table 1).

In a retrospective analysis of infants presenting to a Japanese tertiary center, the use of proactive topical steroids within 4 months duration of moderate-severe AD vs commencing after 4 months duration of moderate-severe AD resulted in 2-fold reduction by 24 months.[79] The same group subsequently performed a randomized controlled trial using proactive topical steroids in children with mild AD within 7 to 13 weeks of age including nonaffected areas in the intervention arm and revealed a 25% reduction in egg allergy by 6 months of age. However, it also revealed a significant reduction in weight and length in the intervention arm.[79] This highlights important safety concerns with regard to use of potent topical steroids to the whole body (even areas without visible AD) for future studies.

Alternative anti-inflammatory topical therapies include TCIs licensed to treat AD in children 2 years of age and older in Europe and in the United States, tacrolimus 0.03% ointment and pimecrolimus 1% cream. However, in Canada, the latter has also been approved for 3 months of age and older. The use of these treatments in children younger than 2 years of age is off label, although, very common.[77] Proactive therapy with topical corticosteroid and TCI against reactive treatment has proven to prolong the interval between flares and to benefit from a lower barrier disruption.[75,77] However, it has 2 potential problematic aspects to consider: the lack of knowledge regarding long-term safety and adverse effects in children younger than 2 years of age and the uncertain duration of this regimen.[75] There are, however, 10-year safety data revealing no increased risk of cancer with the use of tacrolimus 0.03% and 0.1% ointment in children with initiated therapy before 2 years[80] and a recent systematic review revealing little to no risk of cancer in pediatric or adult patients treated with TCI.[81]

Probiotics and Prebiotics Topical Application for the Prevention of Atopic Dermatitis and Food Allergy

Multiple factors influenced microbial diversity; however, to date, the immunomodulatory effect of topical application of "biotics" is still inconclusive.[77] Prebiotic mixtures have been found to be beneficial in preventing AD,[76] and probiotics containing lactobacillus mixtures, among others, also found to improve AD in some studies, and in others made little or no difference.[76,82] This may be due to differences in the strains of probiotics, the characteristics of the host, the timing of the application, and other risk factors, including air pollution, climate, psychosocial factors, and diet.

To date, we still have little evidence regarding the role probiotics have in FA prevention; however, this route presents an interesting and promising alternative approach to address the gut-skin axis in patients with AD. Future research should focus on this to reach definitive conclusions.

Table 1
Comparison of Skin-Targeted Therapies for Food Allergy Prevention

Variables	Emollients/moisturizers	Topical corticosteroids[1,2]						Topical immunomodulators		
		Group I	Group II	Group III	Group IV	Group V	Groups VI-VII	Tacrolimus 0.03% Low dose	Tacrolimus 0.1% High dose	Pimecrolimus
Age restrictions (children < 2 y old)	No	Under Specialist Supervision			Yes			Off-label use	No	Off-label use
Skin application	Body and face	Body	Body and face		Body and face			Body and face		Body and face
Application schedule	BD	OD						OD or BD		
Proactive therapy for prevention of eczema flares[3,4,5]	NA	No	Yes	Yes[3,a]		No		Yes		No[4]/Yes[5]
Short-term treatment	Yes	Yes						Yes		
Long-term treatment[4,5,6]	Yes	No	No	No	Yes		No	Yes		Yes
Benefits preventing FA	Inconclusive[7]	Inconclusive		Yes[8,b]	Inconclusive			Inconclusive		Inconclusive
Common adverse effects	May contain allergenic plant proteins Skin infections	Skin atrophy Telangiectasia Stretch marks Growth restriction in infancy			Skin atrophy Telangiectasia Stretch marks			Site burning Irritation Skin infections		

Abbreviations: AD, atopic dermatitis; BD, twice daily; FA, food allergy; NA, non-applicable; PACI, Prevention of Allergy via Cutaneous Intervention.
[a]In Reference 3: Fluticasone propionate 0.05% is considered medium potency in the United States (Reference 2). However, the same topical corticosteroid is considered a potent corticosteroid in the United Kingdom (Available at www.medicines.org.uk/emc/files/pil.9364.pdf).
[b]The PACI study: Betamethasone was used in this study to evaluate whether an enhanced early skin treatment for AD in infants reduces food allergy. Results revealed that the enhanced treatment significantly reduced hen's egg allergy compared with the conventional treatment. Please note that betamethasone valerate is considered strong (0.12% cream: Reference 1) and/or medium potency in the United States (0.1% cream: References 2 and 7), but in the United Kingdom is considered a potent topical corticosteroid (available at https://www.medicines.org.uk/emc/product/929/smpc#about-medicine).

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7. Adapted from: Kelleher MM, Phillips R, Brown SJ, Cro S, Cornelius V, Carlsen KCL, et al. Skin care interventions in infants for preventing eczema and food allergy. Cochrane Database Syst Rev. 2022;11(11):CD013534.
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Novel Skin-Targeted Therapies

The currently available data have propelled the skin as a potential immunomodulatory organ for treating FAs. A better understanding of the progression of AD has facilitated and triggered the surge of innovative treatments directed toward pathologic pathways. In this sense, since Palmer et al[32] revealed that FLG loss-of-function mutations represented the most critical genetic risk linked to AD, hundreds of mutations have been identified.[83]

Potential therapies involving FLG expression include the following: "read-through" drugs, direct replacement of FLG, indirect replacement by topical application of FLG metabolites, and inhibition of cytokine-mediated FLG down-regulation which includes interleukin and janus kinases inhibitors.[84] The "read-through" drugs manage gene expression by acting over regulatory elements, inhibiting a determined mutation, and subsequently enabling the adequate reading frame, which results in the generation of full-length FLG protein.[85] These drugs are patented but not yet available.[86] The topical application of FLG metabolites such as UCA and pyrrolidone carboxylic acid is considered an indirect FLG replacement that could preserve the permeability of the barrier function.[85] Particularly, the use of 5% cis-UCA cream[87] has been confirmed as an efficient and safe option for patients with mild-to-moderate AD.

FLG down-regulation is currently understood to be secondary to uncontrolled expression of IL-4 and IL-13 (T_H2) and IL-22 (T_H22). Other cytokines involved in FLG deficiency are IL-20, IL-24, IL-25, IL-31, and IL-33, but the corresponding mechanisms still need to be understood. Conversely, the up-regulation of FLG expression is increased by activating a ligand-activated transcription factor, an aryl hydrocarbon receptor.[84,88,89]

Furthermore, treatment strategies that are novel and targeted toward the skin, such as epicutaneous immunotherapy (Table 2) and skin-targeted gene therapy, aim to manage and prevent complications of allergic diseases.

Skin-Targeted Gene Therapy

Skin-targeted gene therapy is an effective and convenient treatment option for the prevention and treatment of FA which is achieved by delivering the therapeutic protein or the allergen in the form of plasmid DNA in vivo to modulate allergic immune responses. Adenovirus remains to be the most extensively used gene transfer

Table 2
Clinical Trials Using EPIT for the Treatment of FA

Title	NCT	Phase	PMID(s)	Finding	Size
Efficacy and Safety of Several Doses of Viaskin Peanut in Adults and Children With Peanut Allergy (VIPES)	NCT01675882	2b	29136445	Increase in reaction threshold in those who received peanut EPIT (250 mg Viaskin [VP250]) compared with placebo after 52 wk of treatment	221 individuals with peanut allergy between 6 and 55 y old across 22 centers in the United States and Europe
Peanut Epicutaneous Phase II Immunotherapy Clinical Trial	NCT01904604	2	28091362 33290772	Peanut EPIT was associated with significant desensitization and immunologic changes after 52 wk of treatment in those who received 100 mg (VP100) or VP250 doses, compared with placebo EPIT, with the highest product adherence and response observed within the younger children. Open-label extension revealed VP250 was well tolerated, and desensitization persisted between weeks 52 and 130, though treatment success was predominantly observed in the younger cohort. EPIT increased IgG4 but no change in IgE or basophil activation.	75 individuals with peanut allergy between 4 and 25 y old recruited across 5 clinical CoFAR sites in the United States.
Efficacy and Safety of Viaskin Peanut in Children With IgE-Mediated Peanut Allergy (PEPITES)	NCT02636699	3	30794314	After 12 mo of treatment, 25.3% of peanut EPIT-treated participants and 13.6% of placebo-treated participants reached an eliciting dose of ≥1000 mg peanut.	356 individuals with peanut allergy between 4 and 11 years of age recruited across 31 different sites in the United States, Canada, Australia, and Europe
Follow-up of the PEPITES Study to Evaluate Long-term Efficacy and Safety of Viaskin Peanut in Children (PEOPLE)	NCT03013517	3	32659313	After 24 mo of open-label extension of peanut EPIT, 51.8% of participants reached an eliciting dose of ≥1000 mg peanut in comparison to 40.4% who reached this does before the open-label extension.	213 individuals with peanut allergy who received peanut EPIT in the PEPITES trial[a]
Safety Study of Viaskin Peanut to Treat Peanut Allergy (REALISE)	NCT02916446	3	4848381	VP250 was well tolerated in children with peanut allergy, although local skin reactions were reported in all the children receiving VP250 and 83.8% of those on placebo.	399 individuals with peanut allergy between 4 and 11 years of age recruited across 32 sites in the United States and Canada
Safety and Efficacy Study of Viaskin Peanut in Peanut-allergic Young Children 1-3 Years of Age (EPITOPE)	NCT03211247	3	37163622	After 12 mo of treatment, 67% of VP250-treated participants and 33.5% of placebo-treated participants passed a peanut OFC to ≥1000 mg peanut. Adverse reactions were found in all VP250 participants and 99.2% of placebo-treated participants.	414 individuals with peanut allergy between 1 and 4 years old recruited across 51 sites in the United States, Canada, Australia, and Europe

Abbreviations: CoFAR, Consortium of Food Allergy Research; EPIT, epicutaneous immunotherapy; FA, food allergy; OFC, oral food challenge.
[a]Only 141 received OFCs and are included in the data.[2]
References for Table 2:
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vector and has been found to be highly tolerable and efficient. One such example includes a recent study in murine model to assess the potential benefit of single-dose of adeno-associated virus (AAV) vector gene immunotherapy to treat FA.[90,91] In this study, AAV vectors expressing ovalbumin (OVA) was injected before or after epicutaneous sensitization with OVA. The study revealed that mice treated with AAV-OVA vector were protected from allergy sensitization and had significant reduction in anaphylaxis. Furthermore, AAV gene immunotherapy resulted in induction of OVA-specific T regulatory cells, induction of IL-10, and reduction in IL-13. In addition, while a phase 1, randomized, placebo-controlled study is currently investigating the safety, tolerability, and immune response of intradermal administration of plasmid DNA encoding peanut allergens (ASP0892),[90] it has been proposed that plasmid DNA vaccination can activate natural killer cells that produce interferon gamma, influencing skewing of T helper cell responses.[92] Further studies are warranted to further investigate the potential of gene therapies for the treatment of FAs.

Conclusion

The importance of skin in our biologic defense, its critical role in preventing environmental agents (eg, microbes and allergens) from penetrating the human body, and its response to microbial pathogens are well established. Skin barrier disruption and dysfunction is the initial step in the development of AD, the most common, complex, chronic inflammatory skin condition.

Despite the long-recognized association between AD and the subsequent development of other allergic diseases, the mechanistic link between AD and allergic disease pathogenesis still needs to be fully understood. It is also evident that allergic disease, particularly FA, may trigger or exacerbate AD, so the relationship is complex and results in a feed-forward loop of allergic disease progression.[93] Given the central role of AD, the skin barrier, and skin host immune responses in allergic disease pathogenesis, it is not surprising that there is increasing interest in interventions targeting the skin, including enhancing the skin barrier and optimizing the skin biome. Studies focused on strengthening the skin barrier using emollients to prevent AD and FA have been contradictory rather than conclusive. Recent studies using topical probiotics have shown promise in preventing and treating AD through the modulation of host immune responses. However, there have also been conflicting results regarding the clinical effects of probiotics in patients with AD.

Dysregulation of neuroimmune circuits plays a critical role in the pathophysiology of AD, causing inflammation, pruritus, pain, and barrier dysfunction. Sensory nerves can also be activated by environmental or endogenous trigger factors, and on stimulation, sensory nerve endings release neuromediators, which contribute to barrier dysfunction and inflammation propagating itch. Thus, neuroimmune circuits may be key targets to control pruritus in AD, which would reduce the itch-scratch cycle, which we know increases TSLP and mast cell expansion in the gut.[94] Given the complex environmental and host factors that promote AD and allergic disease, future research is needed that is multi- and cross-disciplinary and brings together leaders in allergy, immunology, dermatology, microbiology, neurology, neuroimmunology, genetics, environmental health, nutrition and gastrointestinal health, and epidemiology to work as seamless teams. Understanding how the immune system, neuroimmune

circuits, environmental factors, genetics, and microbiome coordinate pathologic mechanisms that underlie these common disorders will be necessary to advance the field.

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