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CME Review

Constant vigilance! Managing threats to the skin barrier

Vanessa Chu, MD*; Peck Y. Ong, MD†,‡

* Department of Pediatrics, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California
† Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles, Los Angeles, California
‡ Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California

Key Messages

- Skin barrier defect is a primary cause of atopic dermatitis (AD) and predisposes to cutaneous inflammation, infectious complications, and food allergy.
- The current approach in managing skin barrier defects in AD includes daily skin hydration, moisturization, and timely use of anti-inflammatory medications.
- Lipid barrier dysregulation in barrier defects precedes the development of AD: these changes include a decrease in lipids containing long-chain fatty acids and esterified omega sphingosine-ceramides but an increase in lipids containing short-chain fatty acids.
- These barrier defects provide an opportunity for the prediction and intervention of AD development during infancy.

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ABSTRACT

Objective: Skin barrier defects are one of the primary causes of atopic dermatitis (AD). The basis of skin barrier defects in AD is due to a deficiency in various barrier proteins including filaggrin, involucrin, claudins, and lipids such as ceramide, fatty acids, and cholesterol. This review updates a more detailed lipid dysregulation in the skin barrier of AD based on recent lipidomic analysis. The clinical implications, treatments, prevention, and predictive capability of skin barrier defects are also reviewed.
Data Sources: Published literature obtained through PubMed searches.
Study Selections: Studies relevant to the mechanisms, clinical implications, treatments, prevention, and predictors of AD development.
Results: Skin barrier defects contribute to transepidermal water loss, infections, IgE sensitizations, and cutaneous inflammation in AD. Preventive treatments include daily hydration and application of moisturizers. Because skin barrier defects precede the development of AD, they provide an opportunity for prediction and intervention.
Conclusion: Skin barrier defects play an important role in the comorbidities of AD including infectious complications, disease flare, and allergic diathesis. Current research focuses on prevention and prediction of AD development.

Introduction

Stratum corneum is the outermost layer of the epidermis consisting of dead corneocytes and intercellular lipids which provides a hydrophobic barrier to protect the human body from water loss, pathogens, irritants, and allergens. The intercellular lipids are composed of ceramides (CERs), cholesterol, and fatty acids (FAs). In atopic dermatitis (AD) nonlesional and lesional skin, it has been long known that it is deficient in these lipids.[1] In addition, skin barrier proteins including filaggrin, involucrin, and claudins (-1 and -3) are deficient in AD.[2] The deficiency of these molecules in AD predisposes patients to external threats including microbial pathogens and allergens, resulting in cutaneous inflammation. The association between AD and loss-of-function mutations in the filaggrin genes including R501X and 2282del4 supports skin barrier defects as one of the primary causes of AD.[3]

Address correspondence to: Peck Y. Ong, MD, Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles, 4650, Sunset Boulevard, MS# 75, Los Angeles, CA 90027. E-mail: pyong@chla.usc.edu.

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and be able to apply new information to their own practices.

Learning Objectives

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

- Summarize the skin barrier defects in atopic dermatitis (AD).
- Assess clinical implications of skin barrier defects in AD patients.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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More recently, detailed lipidomic analyses of the stratum corneum based on skin tape stripping in AD have further improved our understanding of the lipid barrier defects in AD.[4,5] In both lesional and nonlesional samples, pediatric patients with AD had increased proportion of nonsaturated CERs, lipophosphatidylcholine, and sphingomyelin with short-chain FAs (SCFAs). There was a corresponding decrease in long-chain species compared with in healthy children, in whom the most prevalent CERs contained long-chain FAs (LCFAs) between C24 and C26. The ratio of lipophosphatidylcholine with LCFAs to SCFAs and the ratio of esterified omega-hydroxy FAs and sphingosine CERs (EOS-CERs) to total nonsaturated CERs negatively correlated with transepidermal water loss (TEWL). These differences were more prominent in lesional compared with in nonlesional areas. The FA chain length in lipids affects the membrane architecture and permeability. Moreover, SCFAs (C16-18) provide less effective interactions with other lipid chains, which leads to aberrant structural organization in the extracellular layers that affect barrier function and results in increased TEWL. The lipid barrier dysregulation in AD may be explained by interleukin (IL)-4/IL-13–mediated down-regulation of FA elongases 3 and 6 (ELOVL3 and ELOVL6), elongase 1, acid-sphingomyelinase, and B-glucocerebrosidase, which are involved in the synthesis of LCFAs and CERs, leading to increased short-chain species in AD skin.[5]

The Dysregulation of Lipid Skin Barrier by *Staphylococcus aureus*

More than 90% of AD lesions are colonized by *Staphylococcus aureus* (*S aureus*), as compared with approximately 10% in healthy skin.[6] In addition to barrier defects, the predominance of *S aureus* in AD may be partly explained by IL-4/IL-13–mediated suppression of host antimicrobial peptides.[7] Furthermore, the dendritic cells of patients with AD produce a lower amount of interferon-$\propto$.[8] The colonization of *S aureus* not only predisposes to an increased prevalence of infectious complications in AD but also contributes to the inflammation of AD through production of staphylococcal superantigens. Among those colonized, it is estimated that 10% to 30% of isolates are methicillin-resistant *S aureus* (MRSA), which are more virulent and toxigenic strains of *S aureus*.[9]

In addition to an increased prevalence of *S aureus*, AD skin was found to have a dysbiosis with decreased proportions of *Streptococcus*, coagulase-negative *Staphylococcus* (CoNS), *Acinetobacter, Corynebacterium*, and *Propionibacterium* and loss of bacterial diversity.[4] Commensal CoNS may help in regulating host immune response by reducing inflammation and protecting against microbial pathogens.[8] *S epidermidis* modulates host cytotoxic cells in wound repair and regulatory T cells in immune tolerance. It also prevents TLR-3–mediated inflammation by producing a lipoteichoic acid that up-regulates antimicrobial peptides. Other CoNS including *S lugdunensis* and *S hominis* produce antimicrobial factors or proteases that prevent biofilm formation and exhibit bactericidal activity against *S aureus*.

A positive association was found between the FA chain lengths of CERs and lipophosphatidylcholine with *Corynebactium* and negative association with *Staphylococcus*. Overall, the chain length, type of hydroxylation, and saturation of stratum corneum lipids affect the microbiome of the skin, and dysbiosis can lead to aberrant lipid profiles in AD skin.[4] These findings are consistent with previous results in adult patients with AD that LCFAs in CERs were associated with an increase in *Propionibacteria* and *Corynebacterium*.[10]

In pediatric patients with AD, it was found that TEWL was significantly increased in AD lesions colonized with MRSA, as compared with those colonized with methicillin-sensitive *S aureus* (MSSA) and those without *S aureus*.[11] AD severity, assessed by SCORing AD, was significantly higher in patients colonized with MRSA, as compared with those without *S aureus*, whereas there was no difference in AD severity between those colonized with MSSA vs those without *S aureus*. In MSSA-colonized skin, level of sphingomyelins N-acylated with palmitic acid (C16) was significantly increased, with corresponding decrease in very LCFAs (VLCFAs) containing sphingomyelins (C20 and C22) and lipophosphatidylcholines (C26 and C28), as compared with skin without *S aureus* colonization.[11] However, in AD skin colonized with MRSA, various SCFAs including nonhydroxy FA and sphingosine CERs (Non-hydroxy fatty acids and sphingosine ceremides (NS-CER)) N acylated with C16 to C22 FAs, sphingomyelins N-acylated with C16 and C17 FAs, and lipophosphatidylcholines with C16 to C18 FAs were significantly increased as compared with AD skin colonized with MSSA and AD skin without *S aureus* colonization.[11] Furthermore, VLCFAs containing NS-CERs (C26-30) and sphingomyelins (FA lengths C24 and C28) were found to be decreased in AD skin colonized with MRSA. These data suggest that *S aureus* colonization is associated with an increase in SCFAs but a decrease in LCFAs in the lipid composition of the skin barrier. This effect is most pronounced in MRSA-colonized AD skin. The effects of how Staphylococci exposure affects the production of Elongation of Very Long (ELOVL) chain fatty acids in keratinocytes were further studied by quantifying expression of these enzymes after stimulation with MSSA/MRSA, as compared with *S epidermidis*.[11] Gene expression of ELOVL5 was increased in *S epidermidis*-stimulated keratinocytes, whereas MSSA significantly inhibited ELOVL3 expression, and MRSA inhibited both ELOVL3 and ELOVL4.[11] MSSA-induced IL-1β, TNF-α, and IL-6 inhibit ELOVL3, which leads to an increase in SCFAs, whereas MRSA-induced IL-33 inhibits both ELOVL3 and ELOVL4, leading to both an increase in SCFAs and a decrease in LCFAs. The effects of toxins produced by MSSA/MRSA were analyzed as well.[11] Notably, phenol-soluble modulin alpha 3 inhibited gene expression of ELOVL3.[11]

In summary, *S aureus* affects the lipid composition of the skin barrier through its effect on cytokines or toxin production which inhibits ELOVL and results in an increase in ratio of SCFAs to LCFAs,[4,11] which is associated with worsening of skin barrier functions.[5]

Comorbidities Associated With Skin Barrier Defects in Atopic Dermatitis

Infectious Complications

Skin barrier defects contribute to an increased prevalence of skin and soft tissue infections (SSTIs) caused by *S aureus*.[8] Common SSTIs in AD include impetigo, cellulitis, and skin abscesses. SSTIs in patients with AD may lead to systemic infections which include bacteremia, osteomyelitis, septic arthritis/bursitis, and endocarditis. In addition to *S aureus, Streptococcus pyogenes* may cause SSTIs in patients with AD.

Skin barrier defects also increase the risk of viral infections in AD. Eczema herpeticum (EH) is caused by herpes simplex virus-1, which is a potentially life-threatening infectious complication in patients with AD. Other viral skin infections in AD include eczema coxsackium, which is caused by coxsackie viruses in the enterovirus family; molluscum contagiosum, which is caused by a poxvirus in the Molluscipoxvirus subfamily; and eczema vaccinatum (EV), which is caused by live vaccinia virus in smallpox vaccines. Comparing the lipid composition of nonlesional stratum corneum for patients with recurrent EH vs patients with AD without a history of EH and healthy controls, the former has an increased proportion of nonhydroxy SCFAs NS-CERs but a decrease in the proportion of long-chain NS-CERs.[12] There was an overall decrease in the ratio of EOS-CERs to NS-CERs in patients with AD with recurrent EH, as compared with patients with AD without a history of EH and healthy controls. In addition, patients with EH had an increased total sphingomyelin content and levels of 17-carbon sphingosine, suggesting that this subset of patients has an increased turnover of sphingolipids in the skin and an increased level of free sphingosines. Plasma sphingosine-1-phophate (S1P) to CER ratio was found to be significantly increased in patients with EH. On the basis of 1 patient with AD who subsequently

developed EH, it was confirmed that high plasma S1P-to-CER ratio preexisted before the development of EH. Of interest, patients with a history of EV also had increased plasma S1P and NS-CER, as compared with patients with AD without a history of EV. An increase in systemic S1P likely contributes to the replication of these viruses, as revealed by inhibiting S1P lyase, which led to an increase in S1P turnover and a doubling rate of herpes simplex virus-1 infection in keratinocytes.

Development of Food Allergy

The prevalence of food allergy in a healthy pediatric population is approximately 1 in 20 subjects, whereas in a pediatric population with AD, the prevalence of food allergy is at least 1 in 5 patients.[13] In pediatric patients with moderate-to-severe AD, the prevalence of food allergy increases to 1 in 3 patients. This trend is consistent with the skin being the sensitizing organ in patients with AD. This hypothesis is supported by multiple animal studies. The mice that received intradermal injection of thymic stromal lymphopoietin (TSLP) and ovalbumin subsequently developed serum-specific IgE to ovalbumin and diarrhea when fed ovalbumin.[14] In another mouse model, tape stripping was applied to simulate skin barrier defects of AD. Ovalbumin was then applied epicutaneously for 3 weeks.[15] These mice also developed serum-specific IgE. These observations were reproducible using a combination of epicutaneous application of both ovalbumin and vitamin D. This model led to increased production of cutaneous TSLP and subsequently serum-specific IgE to ovalbumin.[16]

Clinical data from the Mechanisms of Progression from Atopic Dermatitis to Asthma in Children (MPAACH) study revealed that the increase in skin barrier defects in infants with AD correlates with positive skin test results to peanut, egg, and pets.[17] The strong association between AD and food allergy suggests that these 2 conditions likely share common genetic determinants such as skin barrier defects and IL-4 receptor alpha chain polymorphisms.[18] Inherent skin barrier defects render AD skin susceptible to allergen penetration and trigger epithelial alarmins such as IL-25, IL-33, and TSLP, which activate the type 2 immune response and cause subsequent allergic sensitization. However, most children with AD do not have food allergy. Apart from AD severity as a risk factor for food allergy, children with AD and food allergy likely constitute a unique endotype in skin barrier defects. A well-controlled study revealed that children with AD and food allergy had significantly worse TEWL after tape stripping in their nonlesional skin than patients with AD without food allergy.[19] It was further revealed that *S aureus* colonization on nonlesional AD skin correlates positively with TEWL only in patients with food allergy, further suggesting the collaboration between this bacteria and unique skin barrier defects in the pathogenesis of food allergy in children with AD.

Children with AD and food allergy have been found to express a distinct group of epidermal proteins that are designated as the principal component 1 (PC1) proteins, as compared with healthy children and children with AD but without food allergy.[20] A positive correlation was observed between PC1 protein expression and TEWL after tape stripping. Children with food allergy were found to have the highest TEWL, followed by children with AD but without food allergy and healthy children. Similarly, significant positive correlations were found between the expression of PC1 proteins and total IgE, specific food and aeroallergen IgE among these groups of children. These data further support the role of skin barrier defects in a clinically distinct phenotype of children with both AD and food allergy.

Atopic Dermatitis Triggered by Aeroallergens and Staphylococcus aureus

It has been well-established that aeroallergens may worsen AD.[21] A double-blind, placebo-controlled study revealed that AD worsened significantly in patients who were exposed to grass pollens.[22] The worsening was restricted only to air-exposed skin areas, suggesting a direct skin contact with aeroallergens is needed for the adverse effects of aeroallergens. Aeroallergens likely enter AD skin through barrier defects, and the binding of aeroallergen/specific IgE complex by high-affinity IgE receptor on antigen-presenting cells and subsequent presentation to T cells result in a further increased production of IL-4/IL-13 and AD inflammation. Other potential aeroallergen triggers include house dust mites and household furry pets.

In addition to causing infectious complications, the colonization of *S aureus* on AD lesions results in a vicious cycle skin barrier dysregulation, inflammation, and proliferation of *S aureus*. Staphylococcal superantigens are presented by antigen-presenting cells to activate T cells through the variable β chain of T cell receptor, resulting in a polyclonal activation of multiple T cell clones and robust cutaneous inflammation. In addition to superantigens, *S aureus* also produces other toxins including staphylococcal α toxin, which leads to keratinocyte cytotoxicity, and *S aureus*-derived second immunoglobulin-binding protein, which induces the production of IL-33 by keratinocytes,[23] further worsening the allergic inflammation of AD.

Treatments

Moisturization and Hydration

To maintain skin barrier functions in AD, it is recommended that patients take a lukewarm bath or shower daily, followed by gentle drying and application of a moisturizer. The choice of moisturizer is dependent on the patient or parent preference. In general, thicker ointment-based moisturizers are preferred as they are better than creams in retaining moisture in the skin. However, older patients may not like the greasy feel or appearance of ointments; therefore, a lighter cream should be used to increase compliance. Prescription moisturizers (ie, barrier repair creams or ointments) have not been proven to be better than over-the-counter petrolatum-based moisturizers.[24]

Dilute Bleach

A previous meta-analysis revealed that 0.005% bleach improved AD severity by 50% in 32% of patients vs 22% of patients who used water bath.[25] There was no significant change in *S aureus* colonization in those using dilute bleach bath, as compared with water bath. This is consistent with the in vitro observation that dilute bleach at 0.005% does not kill nor inhibit *S aureus* growth.[26] Therefore, dilute bleach likely improves AD through a non-antimicrobial mechanism.

A more recent study revealed that dilute bleach bath significantly improved baseline TEWL in the nonlesional skin of patients with AD at 6 and 12 weeks.[27] Initial baseline TEWL was significantly higher in patients with AD, as compared with healthy controls, but by 6 and 12 weeks of dilute bleach treatment, there was no difference between the 2 groups. Stratum corneum integrity was assessed with TEWL after tape stripping. Initial TEWL after tape stripping was significantly higher in the nonlesional skin of patients with AD, as compared with healthy controls. However, by 6 and 12 weeks of dilute bleach treatment, there was no significant difference in TEWL after tape stripping between the 2 groups. This study suggested that dilute bleach at 0.005% likely improves AD by improving skin barrier functions.

Anti-Inflammatory Therapy

It has been well-established that anti-inflammatory treatments improve skin barrier functions in AD. Both topical corticosteroids (TCSs) and calcineurin inhibitors have been found to improve TEWL of patients with AD.[28] The mechanisms on how anti-inflammatory treatments lead to an improvement of skin barrier functions in AD

are not completely understood. It has been found that TCS did not improve the expression of key barrier molecules including filaggrin or natural moisturizing factor.[29] These observations suggest that anti-inflammatory treatments likely improve skin barrier functions through their suppression of atopic inflammation that results in skin barrier dysfunction in AD.[30]

Dupilumab, a monoclonal antibody that blocks both IL-4 and IL-13, improved skin barrier-associated genes including claudins, filaggrin, loricrin, and ELOVL3.[31] Dupilumab also improved the lipid composition of stratum corneum in patients with moderate-to-severe AD by significantly increasing the proportion of NS-CERs with LCFAs (C24-C32) and decreasing NS-CERs with SCFAs (C16).[32] Normalization of stratum corneum EOS-CERs by dupilumab was also observed in these patients. Post-treatment stratum corneum EOS-CER level was comparable with that of healthy subjects. Tralokinumab, an anti −IL-13 monoclonal antibody, reverses the IL-13 suppression of skin barrier genes including filaggrin, loricrin, and ELOVL3 in primary keratinocytes.[33]

Prevention of Skin Barrier Dysfunction

The concept of inherent skin barrier defects as a primary cause of AD presents a potential opportunity for prevention of AD and possibly subsequent development of allergic diathesis including food allergy by early repair of skin barrier defects. The Barrier Enhancement for Eczema Prevention study was a multicenter, randomized, controlled trial in the United Kingdom in which 1394 infants with high risk of allergy were randomized to daily emollient application for 1 year or standard skin care only.[34] This intervention did not prevent eczema development at 2 years of age in high-risk children. There was also no evidence that emollients decreased risk of food allergy. Those in emollient-based group were actually found to have more frequent skin infections. In addition, the Preventing Atopic Dermatitis and ALLergies (PreventADALL) study, which was a population-based, randomized clinical trial in Norway and Sweden, evaluated whether skin emollient application from 2 weeks of age vs no specific skin care advise would decrease development of AD by 12 months of age.[35] Their study also found that early application of emollient did not prevent the development of AD. The reasons for the failure of these trials are not clear, but possibilities include the type of emollient used, delayed use of emollient, lack of adherence, and failure to control skin inflammation.

More recently, Ni Chaoimh et al[36] hypothesized that preventive application of emollient may need to be started earlier than 11 days to 2 weeks of age to be effective. High-risk infants (ie, infants with parental history of atopy) were randomized to application of an emollient within 4 days of birth vs routine standard skin care during the first 8 weeks. The cumulative incidence of AD at 12 months was lower in those in the intervention group vs in control (31.6% vs 43.8%). When the analysis was stratified into those with and without filaggrin mutations, the differences in the development of AD at 12 months between intervention vs control were even larger (33.3% vs 63.6%), suggesting that those with genetic skin barrier defects might benefit most from the intervention. However, none of these comparisons were statistically significant. There was no difference in prevalence of food allergy between the 2 comparison groups.

Inuzuka et al[37] speculated that the inconsistent results of early application of moisturizer to prevent AD may be due to the ingredients of the moisturizers and the frequency of application. Their study consisted of 3 active treatment groups of babies who have parental or sibling history of AD: group A who received a moisturizer called Fam's Baby twice a day vs group B who received Fam's Baby once a day vs group C who received another moisturizer called 2e. At 32 weeks, the prevalence of AD in the 3 respective groups was 55%, 25%, and 50%, respectively. Fam's Baby once daily was clearly better than 2e once daily in preventing AD at 32 weeks. However, the results were limited by the small sample size of the study (n = 20 in each intervention group). In addition, the mechanism(s) for the better efficacy of Fam's Baby compared with 2e remained unclear. It was also unclear why Fam's Baby twice daily was less effective than once daily, given that there was no other cutaneous adverse effect noted. As AD skin is deficient in CER, a more targeted trial using a CER-dominant moisturizer twice daily as compared with standard skin care starting at birth in high-risk infants is ongoing.[38]

Skin Barrier Defects as a Predictor of Atopic Dermatitis and Allergic Comorbidities

Preventive trials of AD and food allergy have mostly involved intervention such as application of moisturizers, which are relatively benign. Proactive use of anti-inflammatory therapy or targeting the microbiome is an emerging concept in modifying the natural history of AD and prevention of allergic comorbidities. These potential treatments include topical anti-inflammatory medications such as TCS, topical calcineurin inhibitors, aryl hydrocarbon receptor modulators, biologics such as dupilumab, and topical bacteriotherapy.[39-42] As these agents may have potential adverse effects in newborn or infants, an accurate method of identifying infants who are at high risk for the development of AD is needed. Most preventive studies have relied mainly on parental history of atopy. Parental history of AD is a stronger predictor than parental history of asthma and allergic rhinitis.[43] Although parental history atopy is a reliable predictor of AD development, the accuracy is still dependent on the recall bias of the parent. Up to 46% of adults could not recall having had AD or eczema during their childhood.[44] Therefore, a more objective laboratory test for predicting the risk of AD development in infants is needed.

The use of a noninvasive method such as the measurement of TEWL has met with variable results.[45] Rehbinder et al[46] found that high TEWL at 3 months was not predictive of AD development at 6 months. In addition to parental history of atopy, risk factors for AD development include dry skin based on physical examination at 3 months, birth by elective caesarean section, and multiparity.

Berdyshev et al[47] performed skin tape stripping in 111 infants at 2 months: 74 with parental history of atopy or parent/sibling with physician-diagnosed AD and 37 without risk factor (control group). At 12 months, the prevalence of AD in the high-risk group was 30% (n = 22) and in the control group was 14% (n = 5). They found that a decreased level of stratum corneum protein-bound ω-hydroxy FA sphingosine CER (OS-CER), a derivative of EOS-CERs, an increased level of unsaturated sphingomyelin, and an increased ratio of SCFAs to LCFAs containing NS-CER with C18 sphingosine at 2 months were predictive of AD development at 12 months. They further confirmed that an increase in stratum corneum TSLP and IL-13 at 2 months were predictive of AD development at 12 months. Overall, they revealed that a combination of family history of atopy, decreased protein-bound OS-CER, and increased unsaturated sphingomyelin and IL-13 was highly predictive of AD development with an odd ratio of 54. A combination of decreased OS protein-bound OS-CER and increased unsaturated sphingomyelin and TSLP was also highly predictive of AD development with an odd ratio of 30. This is in comparison to an odd ratio of 3.1 for filaggrin genes as a predictor of AD development. These findings suggest that early changes in lipid composition of the skin barrier are crucial in the development of AD.

Another noninvasive method, infrared spectroscopy, has also been used to predict AD development recently.[48] Skin dryness, based on the measurement of water content by infrared spectroscopy at 4 weeks predicts AD development at 12 months. This finding corroborates the previous finding of skin dryness by physical examination at 3 months which predicts AD development at 6 months.[46] Other

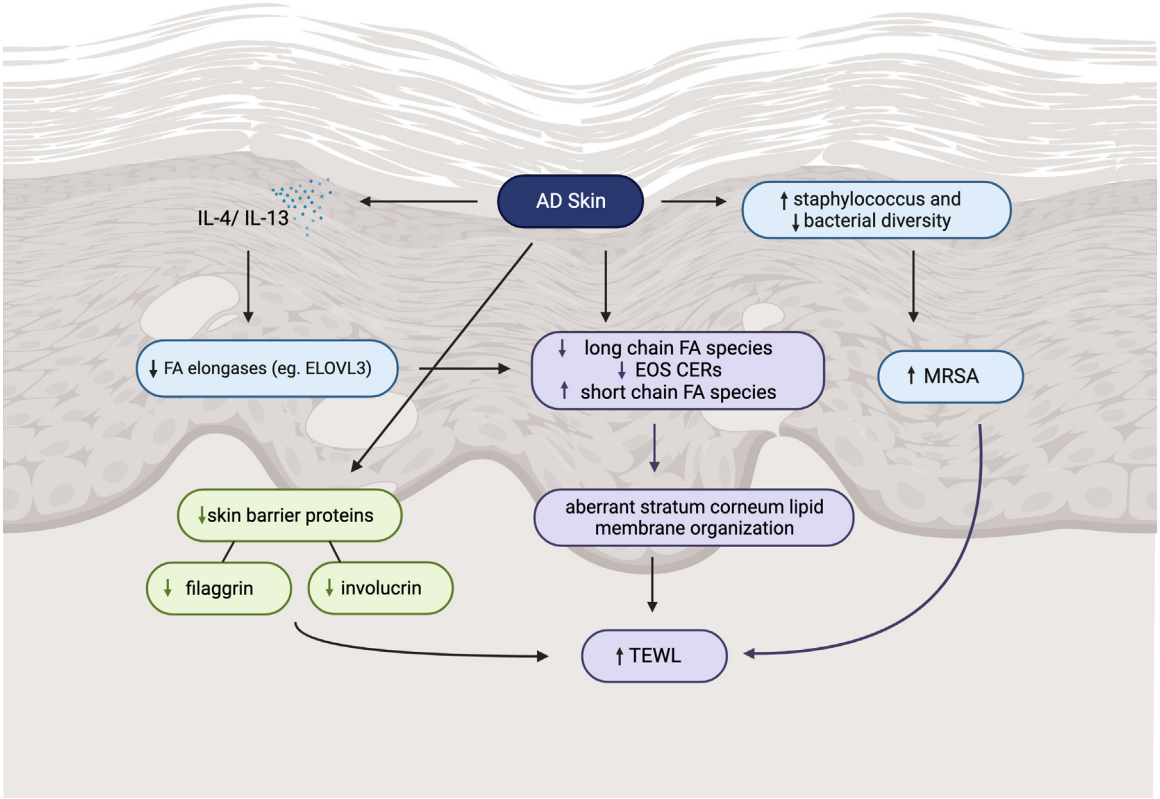

Figure 1. Factors that contribute to skin barrier defects in AD. AD, atopic dermatitis; EOS-CER, esterified omega-hydroxy FAs and sphingosine ceramide; FA, fatty acid; IL, interleukin; MRSA, methicillin-resistant *S aureus*; TEWL, transepidermal water loss.

potential noninvasive methods for detecting skin barrier defects for the prediction of AD development include electrical impedance spectroscopy and optical coherence tomography.[49,50]

Conclusion

Skin barrier defect is one of the primary causes of AD. Detailed analysis of skin barrier proteins and lipidomics supports that skin barrier defects precede the development of AD. Although it has been long known that the lipid composition of skin barrier in patients with AD has a general decrease in CERs, cholesterol, and FAs, further analysis of the lipid composition revealed a reduction of chain length of FAs in various lipids including CERs, sphingomyelins, and lipophosphatidylcholines. A reduction in carbon chain length has been found to correlate with a decrease in skin barrier functions. On the other hand, LCFAs, which are decreased in AD, are crucial for maintaining barrier functions of the skin. In addition to a shortening of FA chain length, AD skin barrier also has a decrease in esterified ω-hydroxy FAs and sphingosine CERs (Fig 1) but an increase in nonhydroxy FAs and sphingosine CERs. These lipid changes make skin barrier less hydrophobic and therefore more susceptible to water loss and environmental insult.[32]

A potential mechanism for the lipid dysregulation in AD skin barrier is a down-regulation of FA elongases, ELOVL3 and ELOVL6, by IL-4 and IL-13. These elongases are involved in the synthesis of LCFAs and CERs. *S aureus* further contributes to lipid dysregulation in AD skin barrier by inhibiting elongases. The effect is particularly more pronounced in more virulent strains such as MRSA, which is associated with a decrease in VLCFA-containing CERs and sphingomyelins and an increase in nonhydroxy FA and sphingosine CERs.

Skin barrier defects predispose patients with AD to an increased prevalence of infectious complications including SSTIs and invasive infections, such as bacteremia, osteomyelitis, and septic arthritis. Skin barrier defects have also been associated with EH, which is a potentially life-threatening viral infection. Increasing evidence suggests that skin barrier defects predispose to increased food IgE sensitization and development of food allergy in infants. However, not all infants with AD and skin barrier defects are predisposed to the development of food allergy. In addition to the severity of AD, more recent data suggest that the unique endotypic features of infants with AD and food allergy include a correlation of TEWL with *S aureus* colonization on nonlesional skin and the expression of epidermal PC1 proteins.

Common environmental triggers for AD include humidity and temperature changes. In addition, aeroallergens and toxins produced by *S aureus* are known triggers via the skin barrier defects. Therefore, a basic tenet of AD management is daily skin care, which consists of at least once-daily bath or shower, followed by gentle drying and application of a moisturizer. In addition, because inflammation is one of the main causes of skin barrier defects in AD, appropriate and timely use of topical or systemic anti-inflammatory medications can further improve skin barrier defects.

As skin barrier defects precede the development of AD and food allergy in infancy, the prevailing view is that repair or normalization of skin barriers could lead to the prevention of these conditions. However, initial well-conducted studies have failed to reveal that early application of moisturizer can prevent AD and food allergy. The reasons for these failures are not completely understood; however, timing of moisturizer application (at birth vs 2 weeks) (Fig 2), types of moisturizers, and frequency of moisturizer applications are current topics of research in various studies.

Because inflammation may play an important role in the regulation of skin barrier defects in AD, the potential use of anti-inflammatory medications to prevent AD and food allergy is an emerging concept in research. However, using these medications in healthy infants requires accurate prediction for the development of AD because of their potential adverse effects. The conventional method

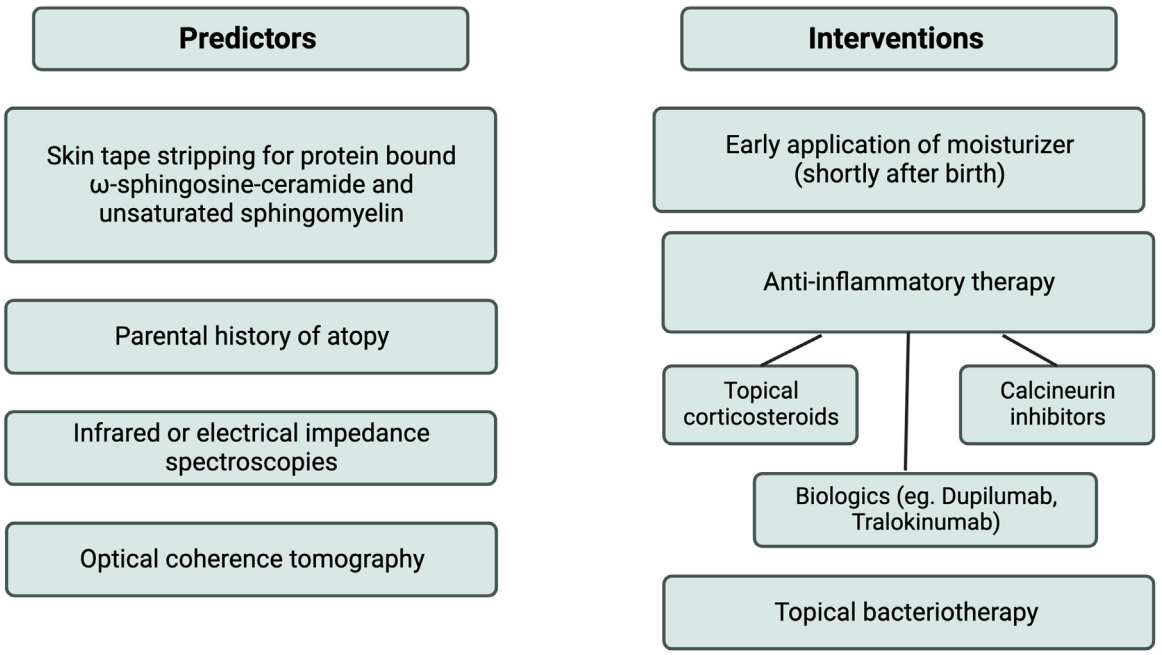

Figure 2. Skin barrier defects as predictors and targets of intervention in AD development. AD, atopic dermatitis.

of predicting the development of AD in infancy has been based on parental history of atopy. Although this method has reasonable predictive value, especially with parental history of AD, it may be flawed by recall bias, as almost half of adults could not recall a childhood history of AD. More objective and noninvasive laboratory testing is needed to complement parental history of atopy in predicting the development of AD. The more recent lipidomic analysis based on skin tape stripping, in combination with family history of atopy, has a predictive odd ratio as high as 54. These findings, together with other noninvasive methods such as infrared spectroscopy, electrical impedance spectroscopy, and optical coherence tomography, hold promise for accurately predicting the development of AD in infancy.

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