Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march

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Skin barrier abnormalities have been suggested to play an essential role in initiation of early atopic dermatitis (AD). Antigen penetration through a compromised barrier likely leads to increased innate immune responses, antigen-presenting cell stimulation, and priming of overt cutaneous disease. In a T/H2-promoting environment, T-cell/B-cell interactions occurring in regional lymph nodes lead to excessive IgE switch. Concurrent redistribution of memory T cells into the circulation not only leads to exacerbation of AD through T-cell skin infiltration but also spreads beyond the skin to initiate the atopic march, which includes food allergy, asthma, and allergic rhinitis. Possible primary interventions to prevent AD are focusing on improving skin barrier integrity, including supplementing barrier function with moisturizers. As for secondary prophylaxis in children with established AD, this can be stratified into prevention of disease exacerbations by using proactive approaches (with either topical corticosteroids or topical calcineurin inhibitors) in mild AD cases or the...
ABNORMALITIES IN PATIENTS WITH AD

Epidermal layers and lipids

The epidermis comprises 4 distinct layers, including the stratum basale, stratum spinosum, stratum granulosum (SG; containing keratohyalin granules [eg, filaggrin [FLG] and loricrin] and lamellar bodies [eg, lipids]), and stratum corneum (SC [ie, the outermost layer]; Fig 1). The SC constitutes corneocytes and the extracellular matrix, creating the classic “bricks and mortar” structure. The corneocytes are mechanically held together by the junctional structures and modified desmosomes (ie, corneodesmosomes). Corneodesmosin, kallikrein-related peptidases, and lymphoepithelial Kazal-type related inhibitor (LEKTI) are all involved in corneodesmosome processing.11 When the extracellular parts of the corneodesmosomes are completely degraded, desquamation occurs.12 Inherited forms of corneodesmosome dysfunction were described, underlining the significance of this structure to an intact skin barrier.11,13,14 Dysregulation of different corneodesmosomal components (eg, desmoglein 1) has been implicated in patients with AD.14

As the major component of the epidermal barrier, the SC harbors antimicrobial, antioxidant, hydration, cohesion, and sensory properties.13 The extracellular matrix is enriched in hydrophobic free fatty acids, cholesterol, and ceramides,15 which are maintained at an optimal ratio.16 Disruption of the lipid composition has been documented in both lesional and nonlesional AD skin.17 Additionally, the TMEM79 gene, which is involved in secretion of lipid-synthesizing lamellar bodies, was shown to be associated with AD.18 These alterations lead to increased TEWL, reduced skin hydration, and impaired barrier function.17,19 Cole et al20 performed a transcriptomic analysis of pediatric AD skin, showing abnormalities in lipid metabolism genes despite lack of FLG mutation, which suggests that lipid abnormalities contribute independently to barrier impairment. Later, a meta-analysis of the AD transcriptome showed significant negative correlations between key epidermal lipids and Tg2 activation.21 Furthermore, the importance of a balanced lipid metabolism to an intact skin barrier is demonstrated by ichthyosis prematurity syndrome. Ichthyosis prematurity syndrome is characterized clinically by nonscaly ichthyosis with atopic manifestations. This autosomal recessive disease is caused by a mutation in the fatty acid transport protein 4 gene (FATP4), which has an essential role in formation of the epidermal barrier during embryogenesis.22

Therapies aimed at restoring cutaneous lipids can prove beneficial for patients with AD. Ceramide-dominant moisturizers have been shown to restore skin barrier integrity.23 Additionally, topical steroids did not show superior efficacy in patients with mild-to-moderate AD compared with over-the-counter petroleum-based or glyceryl rheticin acid–containing emollients.24 A recent evidence-based review evaluating the efficacy of topical and oral oils and fatty acids as treatment for AD concluded that topical oils might be advantageous for AD.25 Liver X receptor (LXR) is a transcription factor that can be activated by a number of small-molecule agonists. In animal models LXR agonists were shown to have beneficial effects on the skin, including increasing

Key words: Atopic dermatitis, atopic march, epidermal barrier, immune dysregulation, microbiome, primary intervention, secondary intervention

Atopic dermatitis (AD) affects 17% to 24% of the pediatric population and 4% to 7% of adults.1 It develops during the first 6 months of life in 45% of children and by 5 years of age in 85% of affected subjects.2 Contrary to prior concepts of outgrowing AD, it is now known that only half of affected children reach disease resolution in adulthood, supporting its chronic nature.3,4 Although it is generally recognized that immune dysregulation (the inside-out hypothesis) contributes to AD pathogenesis and disease perpetuation,5 ample evidence also exists supporting the outside-in or barrier theory of AD, which suggests that a disrupted skin barrier plays a key role in disease initiation.6-8 Supportive evidence for the latter theory includes positive correlations between epidermal permeability (as determined by transepidermal water loss [TEWL]) and disease severity6 and induction of the cytokine cascade secondary to barrier abnormalities.8 Although there are convincing arguments against a primary role of skin barrier defects in AD initiation,10 it is commonly accepted that these defects have a major role in allergic sensitization, opening the door not only for AD but also for the entire atopic march.5 Ongoing efforts are aimed at attempting to identify the optimal primary manipulation that will not only prevent AD but also impede the ensuing atopic march.

In this review we summarize different skin barrier components and their involvement in shaping the AD phenotype and discuss the association between AD and the atopic march. Finally, we present current concepts of potential preventive interventions for AD and its subsequent atopic manifestations.
lamellar lipid levels and corneocyte differentiation and decreasing inflammation. A topical LXR agonist is being tested in patients with AD.

**Tight junctions**

Tight junctions (TJs) are transmembrane proteins critical in establishing keratinocyte adhesion, creating a second physical barrier under the SC. Patients with AD demonstrate deficiency of TJ proteins, particularly in the setting of filaggrin (FLG) mutations. Several TJ proteins, including claudins 1, 8, and 23, and their gene expression are downregulated in the epidermis of patients with AD, probably related to their negative correlation with TH2 cytokine levels. In turn, impaired TJs affect lipids and FLG processing within the epidermis by disturbing skin pH.33

**FLG is a key component of the epidermal differentiation complex**

The epidermal differentiation complex is a cluster of more than 70 genes on chromosome 1q21 encoding for major terminal differentiation proteins involved in formation of the cornified envelope (CE), including those encoding loricrin, involucrin, FLG, small proline-rich proteins, S100 proteins, and late cornified envelope proteins.35,36 Proteins encoded by this complex have a significant functional overlap in maintaining CE integrity.37

FLG (filament-aggregating protein) is the major structural protein of the SC. Numerous proteases and the serine protease inhibitor LEKTI are involved in processing profilaggrin into FLG. FLG degradation products produced in the cornified layer are components of the hygroscopic natural moisturizing factor and are vital for skin hydration, pH maintenance, barrier permeability, and microbial defense.38,39 Loss-of-function mutations in the FLG gene are the most common genetic predisposition for AD. Added to altered pH and increased bacterial growth, reduced ability of the SC to retain water and an impaired CE lead to enhanced allergen and irritant penetration, contributing to AD initiation.40,41 FLG deficiency is associated with earlier onset, increased severity, greater allergen sensitization, and higher infection susceptibility.42-46 FLG mutations are associated with increased allergic sensitization; for example, they were associated with asthma in the context of AD, suggesting that a compromised barrier that facilitates interactions between environmental allergens and antigen-presenting cells (APCs) is a prerequisite to further allergic sensitization, TH2 activation, and IgE switching. Furthermore, lower levels of natural moisturizing factor and increased levels of TEWL have been observed in patients with AD with FLG mutations.
Accumulated data show that FLG expression is amenable to upregulation. However, many obstacles must be overcome to develop a FLG replacement therapy.50 Otuka et al51 identified a bioactive compound (JTC801) that upregulated FLG expression in keratinocyte culture, human skin equivalents, and orally treated mice, attenuating development of AD-like skin inflammation. Furthermore, petrolatum, an inert emollient, improved FLG synthesis in both patients with AD and those without AD, with some associated improvement in inflammation.52 Other FLG replacement therapies were suggested.53-55 Amano et al53 showed that topical application of the Janus kinase inhibitor JTE-005 onto dry skin mouse models improved skin barrier function through signal transducer and activator of transcription 3 inhibition and increased levels of terminal differentiation proteins, such as FLG. Dietary interventions were also shown to increase FLG expression in a mouse AD model.55 An engineered FLG monomer linked to a cell-penetrating peptide showed promising results in cultures and mice.56 The beneficial effect of these compounds in human AD is yet to be determined.

Both lesional and nonlesional AD skin were shown to have low expression levels of FLG, regardless of FLG mutations.57 FLG mutations are only found in 10% to 40% of patients with AD and are rare among African populations, despite their high AD prevalence.47,58-60 Additionally, approximately 40% of FLG mutation carriers never have AD, and most of the children with AD with FLG mutations outgrow their disease.61-63 We characterized the skin profile of 19 children with moderate-to-severe AD aged 3 months to 5 years with AD onset in the previous 6 months.64 We showed that despite the short disease duration, pediatric lesional and nonlesional epidermis in patients with AD is extremely hyperplastic to levels comparable or higher than those in their adult counterparts. Intriguingly, FLG expression was continuous and increased in either lesional or nonlesional pediatric AD skin similar to its expression in skin of healthy children or adults with psoriasis.65 These findings are challenging the notion of FLG as the instigator of AD and the entire atopic march.64 Thus modulation of FLG expression might have a limited value in preventing AD development in high-risk children. Additionally, increased antimicrobial peptide (AMP) expression characterizes pediatric AD skin.64 Thus additional barrier components (eg, lipids and TJs) might be involved in the functional barrier abnormalities and increased TEWL seen in patients with early-onset AD.66,67 Although barrier alterations were established in adults with AD,68-70 further studies are needed in the pediatric population.

The skin barrier is a complex structure, and more detailed description of its components, as well as details regarding additional inherited barrier abnormalities, were recently reviewed by Elias and Wakefield69 and Egawa and Kabashima.71 These proteolytically active allergens aggravate the protease-related barrier defect, increasing allergen penetration and contributing to AD initiation.70

An acidic skin pH (4-6) is necessary to maintain the integrity of the SC, lipid metabolism, epidermal differentiation, and antimicrobial functions.78,79 The baseline skin pH in patients with AD has been found to be neutral/alkaline80 and partially attributed to decreased acidic FLG breakdown products. Jang et al81 evaluated the role of skin pH in the pathogenesis of AD and found that in mouse skin alkalization induced kallikrein-related peptidase 5, leading to corneocyte desquamation, pruritus, and dermatitis. Activation of serine proteases, as induced by increased pH levels, might also lead to Th2 inflammation.82 Acidic pH inhibits the growth of pathogens, such as S aureus, and decreases the expression of staphylococcal surface binding proteins.78,79

Several PAR-2 antagonists are being investigated, and some already show anti-inflammatory barrier-repairing activity.70 Restoring skin acidity might be an adjunct therapeutic strategy in patients with AD. Lee et al83 showed that compared with neutralized cream, acidic cream not only inhibited AD-like skin lesions in mice but also the development of respiratory allergic inflammation.

**MICROBIAL FACTORS AND ANTIMICROBIAL DEFENSES**

Human β-defensin genes (eg, DEFB2, DEFB3, and DEFB4) and cathelicidins (LL-37) are prominent AMPs in the skin.84 Lamellar bodies produced in the SG secreted their contents into the transition between the SG and the SC13 and not only deliver lipids to the SC but also transport AMPs to the intercellular domains, which, together with free fatty acids and low pH, contribute to antimicrobial responses.59 Toll-like receptors (TLRs) are expressed on various cells, including keratinocytes and Langerhans cells (LCs).53 AMPS are induced by keratinocyte and APC TLRs once these are antigenically stimulated.10 TLR2 expression, which is important for both TJ integrity and defense against S aureus infections, is reduced in patients with AD.86,87 Expression of DEFB2 and LL-37 are reduced in AD skin.84 Thus AMP downregulation, altered microbial profile, alkaline pH levels, and cytokine axis deviation all render patients with AD more susceptible to recurrent cutaneous infections.8,86-91

The normal commensal microflora play an essential role in maintaining immune homeostasis.92 Sequencing of the cutaneous microbial composition showed that although normal skin flora harbors a diverse group of bacteria, patients with AD are characterized by dysbiosis that encompasses not only S aureus colonization93 but also reduction of overall microbial diversity.94 S aureus disrupts epidermal integrity through enhanced protease activity95 and downregulation of the terminal differentiation markers keratin 1, keratin 10, loricrin, and...
FLG\textsuperscript{96}. Its superantigens, staphylococcal enterotoxins A or B and toxic shock syndrome toxin 1, play a major role in AD pathogenesis\textsuperscript{97-99} and act as allergens to induce IgE-specific antibodies.\textsuperscript{100} Staphylococcal exotoxins are strong inducers of IL-22,\textsuperscript{101} further contributing to the chronic cutaneous inflammation and abnormal hyperplastic epidermis seen in patients with AD.\textsuperscript{102,103}

Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are host or pathogen-associated molecules that can trigger and perpetuate inflammatory responses.\textsuperscript{104,105} Diverse types of DAMPs and microbe-associated PAMPs are secreted on tissue injury and microbial alterations, respectively.\textsuperscript{106} They bind to pattern recognition receptors, such as TLRs, on APCs to initiate and orchestrate innate immune responses (Fig 1). They were shown to promote TLR activation in inflamed and colonized AD skin,\textsuperscript{107} contributing to T\(\text{H}_2\) sensitization, proinflammatory cytokine release, and amplification of cellular inflammatory responses.\textsuperscript{108}

Complex interplay exits between immune dysregulation and the epidermal barrier defects in patients with AD. T\(\text{H}_2\) (eg, IL-4 and IL-13) and T\(\text{H}_2\) cytokines downregulate epidermal differentiation complex gene expression, promote S\textit{aureus} binding and colonization,\textsuperscript{99,110} and reduce lipid synthesis.\textsuperscript{111-115} A key player in allergic inflammation,\textsuperscript{109} the itch-inducing cytokine TSLP,\textsuperscript{116} thymic stromal lymphopoietin (TSLP), is produced in keratinocytes on antigenic stimulation through a disrupted skin barrier stimulates APCs and induces T\(\text{H}_2\) responses and subsequent atopic manifestations. LCs express FcεRI and the TSLP receptor.\textsuperscript{137-139} The compromised barrier that accompanies AD allows for easier antigen penetration to activate pattern recognition receptors, such as TLRs, and stimulate the release of the epithelium-derived proallergic cytokines IL-25, TSLP, and IL-33 to promote T\(\text{H}_2\) skewing.\textsuperscript{13,140,141} The interaction between T\(\text{H}_2\) responses by these cytokines, IL-25, TSLP, and IL-33 participates in immune responses not only driven by direct effects but also by indirect influence on type 2 ILCs.\textsuperscript{141,144,145}

On antigen binding, IgE-bearing LCs migrate to regional lymph nodes, where they induce T\(\text{H}_2\) production and subsequent B-cell IgE switching. Memory T cells then circulate either back to the skin or to the circulation to induce other atopic disorders (Fig 1).\textsuperscript{146} Myeloid CD11c\textsuperscript{+} DCs and, more significantly, cells that express FcεRI\textsuperscript{+} are highly expressed in the skin of pediatric patients with AD,\textsuperscript{64} supporting a higher propensity to allergic sensitization in the young population. The higher susceptibility of children with AD to a myriad of sensitizations can also be caused by redistribution of LCs, although this is speculative, and better skin characterization is needed.

In mice epicutaneous exposure to peanut initiates T\(\text{H}_2\) responses and food sensitization.\textsuperscript{147} Additionally, associations between peanut allergy and FLG mutations were found in children with or without AD, all supporting barrier integrity significance in early FA development.\textsuperscript{148,149} Increased FA and IgE sensitization were found in children colonized with S\textit{aureus}, suggesting that the microbiome component of the barrier also affects FA development.\textsuperscript{150} IL-9 and especially IL-33 cytokines, which were previously associated with FA and particularly peanut allergy,\textsuperscript{151} are increased in pediatric lesional and nonlesional AD skin.\textsuperscript{152} The role of skin barrier integrity in allergy development has recently emerged from the BASELINE cohort, which showed a high risk of FA by 2 years of age in neonates with increased TEWL in the first 2 months of life irrespective of their AD diagnosis.\textsuperscript{153} Furthermore, abnormal TEWL measurements at age 2 days and even more at age 2 months as a means to detect infants at high risk for AD were able to predict development of AD cutaneous manifestation, regardless of FLG mutation status.\textsuperscript{66} These observations were corroborated by a later study showing that increased forehead TEWL measurements at 1 week of age predict AD development and are associated with increased allergen sensitization.\textsuperscript{67} These results put forward the concept that a functionally impaired skin barrier is a prerequisite to AD and to the entire atopic march, harboring potential for early interventional approaches.

Importantly, TEWL increases in pediatric lesions were shown to reflect the immune activation in patients with early-onset AD. TEWL increased in the skin of pediatric patients with AD were
found to significantly correlate with T_{H17}/T_{H22} and some T_{H2} biomarkers, highlighting the interplay between barrier alterations and cytokine activation in creating the early-onset AD phenotype. Recently, we published data describing activated CD4^{+}/CD8^{+} T-cell frequencies in central memory T (T_{CM}) cells (CCR7^{+}CD45RO^{+} cells, also representing the lymph node reservoir) and effector memory T (T_{EM}) cells (CCR7 CD45RO^{-}) in skin-homing/cutaneous lymphocyte antigen (CLA)^{+} and CLA^{-} (non–skin-homing/systemic) subsets in adults and children with and without AD. Developmentally, when comparing 0- to 3-year-old with 3- to 6-year-old children with AD or children and adults with AD, expression of the midactivation marker inducible T-cell costimulator, which was implicated in stimulating T_{H2} expansion, T-cell/B-cell interaction, and IgE switching, was significantly higher among the systemic/CLA^{-} memory cells of the youngest cohort, supporting early induction of noncutaneous atopic disorders. Increased T_{H2} and low T_{H1} signals, along with increased IgE levels, are found as early as in cord blood of newborns with AD, and thus the temporal order of B-cell activation versus T-cell memory acquisition and the primary pathogenic incident driving AD are not completely clear. Early AD skin phenotype is predominated by T cells and characterized by B-cell paucity, and CD19^{+}CD20^{+} peripheral B cells are dominant in the circulation of children with AD. These observations indicate that early AD has a different phenotype in blood and skin;
although only Tg2 cells are expanded in the circulation.\textsuperscript{153,163} multiple cytokine axes are activated in skin lesions.\textsuperscript{64} At the time active AD develops, approximately 99% of skin-infiltrating lymphocytes are T cells, with a paucity of detectable B cells, suggesting that AD begins primarily as a T cell–driven process in skin.\textsuperscript{162} Thus the atopic march begins with Tg2 expansion and activation in blood and skin promoting IgE-class switching, which fits current immunologic concepts. The fact that allergic manifestations of the atopic march begin months to years after the onset of skin disease might falsely suggest the existence of an allergic “switch” far downstream of skin disease onset. However, molecular onset of IgE class-switching coincides with AD onset (ie, the atopic march skin disease onset. However, molecular onset of IgE sensitization to egg white, skin hydration, and S aureus colonization were also assessed at week 32. No differences were observed in IgE sensitization and S aureus colonization between the intervention and control groups, whereas the intervention group had significantly higher SC hydration.

Mechanisms underlying the preventive effects of moisturizers in high-risk infants are not well understood. Preliminary data show that early moisturizing leads to altered skin microbiome and pH levels in high-risk newborns.\textsuperscript{175} It was shown that petrolatum induces significant upregulation of key AMPs (eg, S100A7/A8/ A9/A12, lipocalin 2, eftin/peptidase inhibitor 3, CCL20, and cathelicidin/LL-37) and innate genes and improves expression of epidermal differentiation markers (FLG and loricrin).\textsuperscript{176} It also reduces T-cell and DC infiltrates only among patients with AD.\textsuperscript{52} These data might in part explain the protective effect against AD development observed in the above studies involving high-risk infants limited by the fact that a diverse group of moisturizers was applied in these cohorts. Future prospective studies that will compare the ability of various moisturizers to prevent AD development in high-risk infants are warranted.

In addition to moisturizing, other primary interventions were studied. Attempts to alter the microbial profile with probiotics had controversial results.\textsuperscript{160,181} Dietary allergen avoidance during pregnancy or lactation in high-risk mothers is not recommended,\textsuperscript{182} and the role of other factors (eg, vaccinations, allergen avoidance, and breast-feeding) in preventing AD is still controversial.\textsuperscript{183,184}

Suppressing inflammatory responses in the skin
Topical anti-inflammatory compounds (corticosteroids and calcineurin inhibitors) are currently prescribed for either active AD or as a component of a proactive treatment for preventing future exacerbations. Despite their potential to primarily suppress skin inflammation, they are not currently recommended as a primary prevention in high-risk nonaffected infants.\textsuperscript{5}

Secondary prevention of the atopic march
Very few data are currently available on secondary prevention of atopic disorders in children with AD. The Early Treatment of the Atopic Child study showed beneficial effects in secondary prevention of asthma with 18 months of treatment with the antihistamine cetirizine in 1- to 2-year-old allergen-sensitized children with AD over a 3-year follow-up.\textsuperscript{185} A large 6-year longitudinal randomized trial, the Study of the Atopic March, followed 1091 infants 3 to 18 months old with an AD duration of 3 months or less and a family history of atopy. Over the first 3 years of the study, infants were randomized to either pimecrolimus cream or placebo, and then for another 3 years, all subjects was open-label treated with pimecrolimus. Mean follow-up time was 2.8 years. Baseline data showed that IgE sensitization increased with AD severity and that increased sIgE levels were already detected at a very young age, suggesting that interventions to prevent the atopic march should be conducted early in infancy.\textsuperscript{186} Results showed increased rates of FA and allergic rhinitis in infants with higher AD severity at baseline.

PREVENTION OF AD AND THE ATOPIC MARCH BY EARLY INTERVENTIONS

Because AD and the subsequent atopic march mostly present in early infancy, primary and secondary prevention should be attempted as early as possible.\textsuperscript{166-168} Fig 3\textsuperscript{24} depicts the concept that cutaneous AD develops possibly in conjunction with allergen penetration through a compromised skin barrier. Subsequently, excess T- and B-cell activation in blood and skin ensue to promote the development of other allergic manifestations. Thus strategies to avoid the first step of the march are different than approaches directed at averting other atopic disorders, and several levels of disease prevention should be distinguished. Although primary prevention involves approaches aimed at inhibiting cutaneous AD development in high-risk infants, secondary prevention harbors tactics intending to halt the resultant atopic march once AD skin involvement is overt.

PRIMARY PREVENTION

Supporting and supplementing barrier function
Moisturizers were shown to improve barrier function, with the additional beneficial effect of reducing inflammatory products.\textsuperscript{52,169-171} Use of moisturizers in premature newborns decreases TEWL, dermatitis severity, and bacterial colonization.\textsuperscript{172-174} An initial small study suggested that petrolatum can be used for primary AD prevention.\textsuperscript{775} Recent cornerstone prospective studies showed that moisturizers significantly reduce rates of AD development. In the first open-label uncontrolled pilot study, Simpson et al\textsuperscript{176} used Cetaphil cream (Galderma Laboratories, Fort Worth, Tex) in 20 high-risk neonates from 1 to 7 days of life, with subsequent follow-up at 1, 6, 12, and 24 months demonstrating protective effects against AD development. A later randomized controlled trial from the same group enrolled 124 high-risk neonates treated daily, with entire-body moisturizing starting within the first 3 weeks of life until age 6 months.\textsuperscript{177} The primary outcome of the cumulative incidence of AD at 6 months showed a 50% relative risk reduction in the treated group. A concomitant randomized controlled trial study from Japan\textsuperscript{178} reported 32% reduction in AD diagnosis at age 32 weeks in 118 high-risk infants who received daily moisturizer since birth. IgE sensitization to egg white, skin hydration, and S aureus colonization were also assessed at week 32. No differences were observed in IgE sensitization and S aureus colonization between the intervention and control groups, whereas the intervention group had significantly higher SC hydration.

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A slightly nonsignificant increase of asthma was observed among the pemicrolinus group, probably secondary to more severe baseline AD. Low patient compliance and lack of mechanistic studies in skin and blood limit the interpretation of this study.

Environmental interventions were also suggested to reduce asthma development in children with AD. Dupilumab, an IL-4 receptor mAb, has shown efficacy in the treatment of asthma and AD. Skin improvement in patients with AD (approximately 70%) was coupled with tissue reversal of the immune and barrier abnormalities, including inflammatory cytokines and epidermal hyperplasia. As discussed above, the epithelium-derived cytokines TSLP, IL-33, and IL-25 promote Th2 responses and are involved in early AD initiation and instigation of other allergic disorders. Thus early blockade of the Th2 axis with dupilumab in patients with established severe AD holds promise for secondary prevention of the atopic march; however, longitudinal studies are needed to prove the efficacy of this approach.

**CONCLUDING REMARKS**

Although accumulated data suggest that primary prevention of AD in high-risk infants (before AD development) might be feasible through intensive use of emollients, blood and skin data from young children with moderate-to-severe AD already show extensive systemic and local immune activation, which likely mandates systemic immune intervention (eg, dupilumab) to effectively treat the disease and prevent the atopic march. Once AD remission has been reached in patients with established disease, proactive therapeutic approaches have shown efficacy in preventing further AD exacerbations. Future longitudinal studies should evaluate the effect of dupilumab and other immune modifiers on changing the course of the atopic march in children with severe AD.

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