

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



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1. To recognize the role of epidermal barrier abnormalities in patients with atopic dermatitis and the subsequent atopic march.
2. To identify primary and secondary interventions that might be helpful in patients with atopic dermatitis.

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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

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prevention of other atopic disorders that will probably mandate systemic immunosuppression in severe AD cases. (J Allergy Clin Immunol 2017;139:1723-34.)

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 using transepidermal water loss [TEWL]) and disease severity⁶ and induction of the cytokine cascade secondary to barrier abnormalities.⁹ 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.³ 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.

SKIN BARRIER ELEMENTS AND THEIR 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} 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

Abbreviations used

AD:	Atopic dermatitis
AMP:	Antimicrobial peptide
APC:	Antigen-presenting cell
CE:	Cornified envelope
CLA:	Cutaneous lymphocyte antigen
DAMP:	Damage-associated molecular pattern
DC:	Dendritic cell
FA:	Food allergy
FLG:	Filaggrin
ILC:	Innate lymphoid cell
LC:	Langerhans cell
LEKTI:	Lymphoepithelial Kazal-type related inhibitor
LXR:	Liver X receptor
PAMP:	Pathogen-associated molecular pattern
PAR:	Protease-activated receptor
SC:	Stratum corneum
SG:	Stratum granulosum
T _{CM} :	Central memory T
T _{EM} :	Effector memory T
TEWL:	Transepidermal water loss
TJ:	Tight junction
TLR:	Toll-like receptor
TSLP:	Thymic stromal lymphopoietin

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 T_H2 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 glycyrrhetic 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

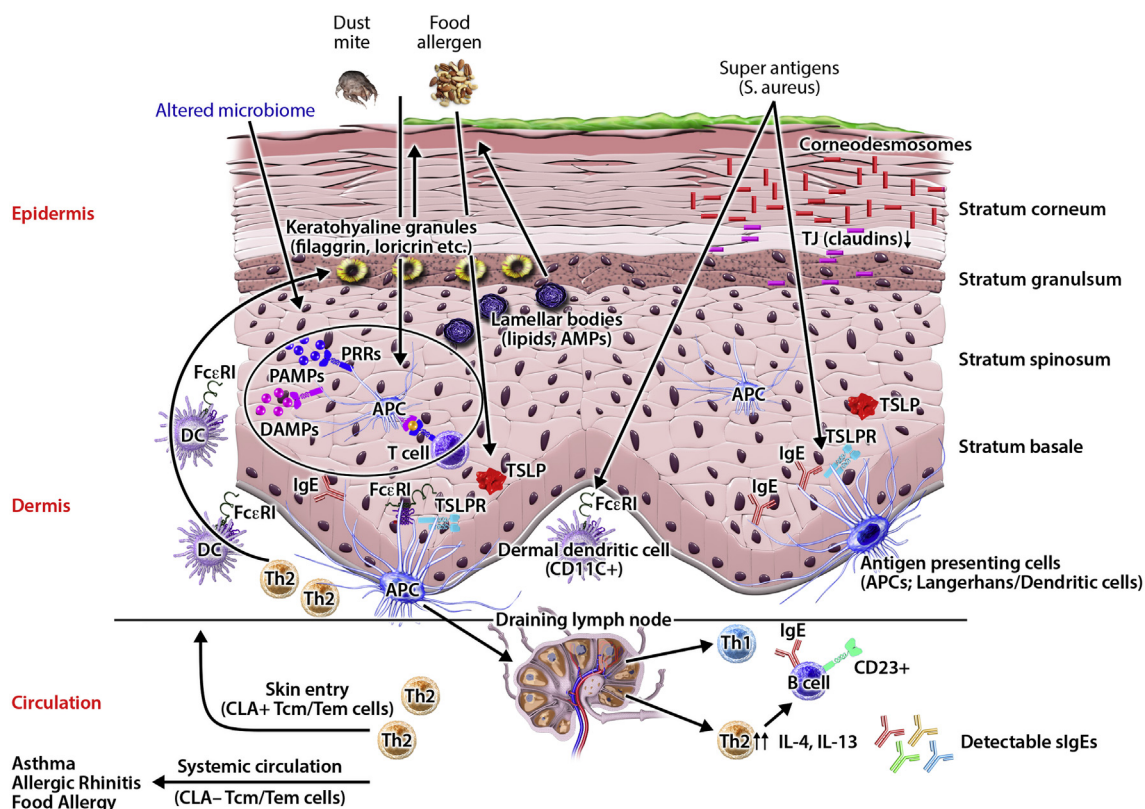


FIG 1. Impaired skin barrier promotes foreign antigen (eg, dust mite and food allergens) penetration and activation of innate immune and pattern recognition receptors. PAMPs and DAMPs are secreted secondary to tissue damage and/or an altered microbial profile to initiate and perpetuate tissue inflammation (zoomed-in area). Concurrently, antigen stimulation leads to T_H2 -promoting cytokine secretion (IL-25, IL-33, and TSLP), consequent IgE- and FcεRI-bearing LCs and dermal DC activation, and migration to regional draining lymph nodes to initiate T_H2 differentiation and B-cell IgE skewing. In turn, T cells circulate back to infiltrate the skin ($CLA^+ T_{EM}/T_{CM}$ cells) or are distributed peripherally ($CLA^- T_{EM}/T_{CM}$ cells) to other end organs to initiate diverse atopic disorders. PRR, Pattern recognition receptor; TSLPR, TSLP receptor.

lamellar lipid levels and corneocyte differentiation and decreasing inflammation.²⁶ 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.²⁷ Patients with AD demonstrate deficiency of TJ proteins, particularly in the setting of filaggrin (FLG) mutations.²⁸ 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 T_H2 cytokine levels.^{21,29-31} A dose-dependent effect of claudin 1 expression was demonstrated on the epithelial barrier and on AD phenotype.³² 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),³⁴ 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.³⁸ 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 sensitization⁴⁶; for example, they were associated with asthma in the context of AD,⁴⁷ suggesting that a compromised barrier that facilitates interactions between environmental allergens and antigen-presenting cells (APCs) is a prerequisite to further allergic sensitization, T_H2 activation, and IgE switching.⁴⁸ Furthermore, lower levels of natural moisturizing factor and increased levels of TEWL have been observed in patients with AD with FLG mutations.^{17,39,47,49}

Accumulated data show that FLG expression is amenable to upregulation. However, many obstacles must be overcome to develop a FLG replacement therapy.⁵⁰ Otsuka 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-052 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,^{31,57,68} 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.¹³

ENVIRONMENTAL FACTORS

Proteases and skin pH

Proteases are widely involved in AD pathogenesis through FLG processing, inflammation regulation, and pruritus. Endogenous skin proteases are regulated by protease inhibitors and are critical in maintaining barrier permeability and homeostasis. They have direct and indirect proteolytic effects through activation of protease-activated receptors (PARs).⁷⁰ PAR-2 is expressed by many cell types in the skin, particularly keratinocytes. Aberrant expression of proteases and PAR-2 was

demonstrated in lesional skin of patients with AD.^{71,72} Exogenous proteases derived from allergens, such as dust mite and cockroaches, and from *Staphylococcus aureus* also affect the epidermal barrier, either directly through proteolytic activity or indirectly through PAR-2 activation, and were implicated in the pathogenesis of different allergic disorders.⁷³⁻⁷⁵ Compromising corneodesmosome and TJ integrity and expression are suggested mechanisms leading to increased epidermal permeability.^{76,77} 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.⁶⁹ Toll-like receptors (TLRs) are expressed on various cells, including keratinocytes and Langerhans cells (LCs).⁸⁵ 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.^{8,88-91}

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

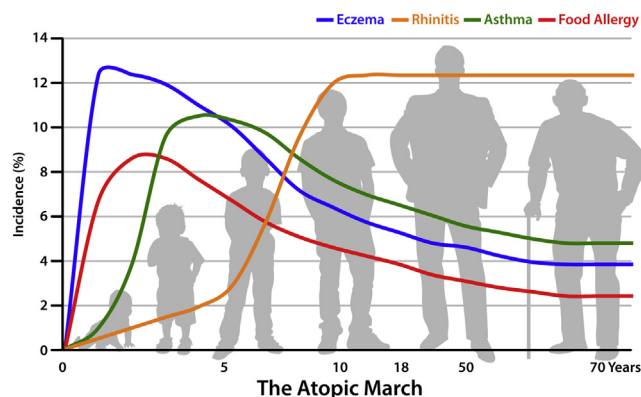


FIG 2. The atopic march. AD prevalence peaks early in infancy, opening the door for consequent development of the atopic march. Development of FA, asthma, and allergic rhinitis in the young toddler age group is common after cutaneous manifestations.

FLG.⁹⁶ Its superantigens, staphylococcal enterotoxins A or B and toxic shock syndrome toxin 1, play a major role in AD pathogenesis⁹⁷⁻⁹⁹ and act as allergens to induce IgE-specific antibodies.¹⁰⁰ Staphylococcal exotoxins are strong inducers of IL-22,¹⁰¹ further contributing to the chronic cutaneous inflammation and abnormal hyperplastic epidermis seen in patients with AD.^{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.^{104,105} Diverse types of DAMPs and microbe-associated PAMPs are secreted on tissue injury and microbial alterations, respectively.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,¹⁰⁷ contributing to T_H2 sensitization, proinflammatory cytokine release, and amplification of cellular inflammatory responses.¹⁰⁸

Complex interplay exists between immune dysregulation and the epidermal barrier defects in patients with AD. T_H2 (eg, IL-4 and IL-13) and T_H22 (IL-22) cytokines downregulate epidermal differentiation complex gene expression, promote *S aureus* binding and colonization,^{109,110} and reduce lipid synthesis.¹¹¹⁻¹¹⁵ A key player in allergic inflammation,¹¹⁶ the itch-inducing cytokine¹¹⁷ thymic stromal lymphopoietin (TSLP), is produced in keratinocytes on antigenic stimulation through a disrupted barrier, further promoting dendritic cell (DC) activation and T_H2 skewing (Fig 1).^{118,119} The interaction between TSLP and LCs is also essential for IgE production in epicutaneous sensitization to food allergens.¹²⁰ The ultimate proof for the ongoing dialog between the barrier and immune dysregulations in patients with AD comes from testing of broad immunosuppressants^{121,122} and immune-targeted therapeutics (dupilumab).¹²³⁻¹²⁶ These studies linked suppression of inflammatory pathways with resolution of the abnormal epidermal barrier in patients with AD.

AD AND THE ATOPIC MARCH

AD, particularly the extrinsic (increased IgE levels) subtype,¹²⁷ is often considered the window to development of other atopic

manifestations, including food allergy (FA), asthma, and allergic rhinitis, that together with AD define the atopic march.^{3,128-131}

Occurrence of asthma, allergic rhinitis, and environmental sensitization increases with age in parallel to the decrease in AD prevalence (Fig 2).¹³²⁻¹³⁴ Positive correlations have been demonstrated between AD severity and the risk of FA, asthma, and allergic rhinitis.^{135,136} The accepted pathogenic concept is that epicutaneous allergen sensitization through an impaired skin barrier stimulates APCs and induces T_H2 responses and subsequent atopic manifestations. LCs express FcεRI and the TSLP receptor.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_H2 skewing.^{13,140,141} Enhancement of OX40 ligand function,¹⁴² a direct effect on naive T-cell differentiation,¹⁴³ APC expansion, and interaction with group 2 innate lymphoid cells (ILCs) are possible mechanisms for promoting T_H2 responses by these cytokines. IL-25, TSLP, and IL-33 participation in immune responses is not only driven by direct effects but also by indirect influence on type 2 ILCs.^{141,144,145}

On antigen binding, IgE-bearing LCs migrate to regional lymph nodes, where they induce T_H2 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).¹⁴⁶ Myeloid CD11c⁺ DCs and, more significantly, cells that express FcεRI⁺ are highly expressed in the skin of pediatric patients with AD,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_H2 responses and food sensitization.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.^{148,149} Increased FA and IgE sensitization were found in children colonized with *S aureus*, suggesting that the microbiome component of the barrier also affects FA development.¹⁵⁰ IL-9 and especially IL-33 cytokines, which were previously associated with FA and particularly peanut allergy,¹⁵¹ are increased in pediatric lesional and nonlesional AD skin.⁶⁴ 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.¹⁵² 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.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.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

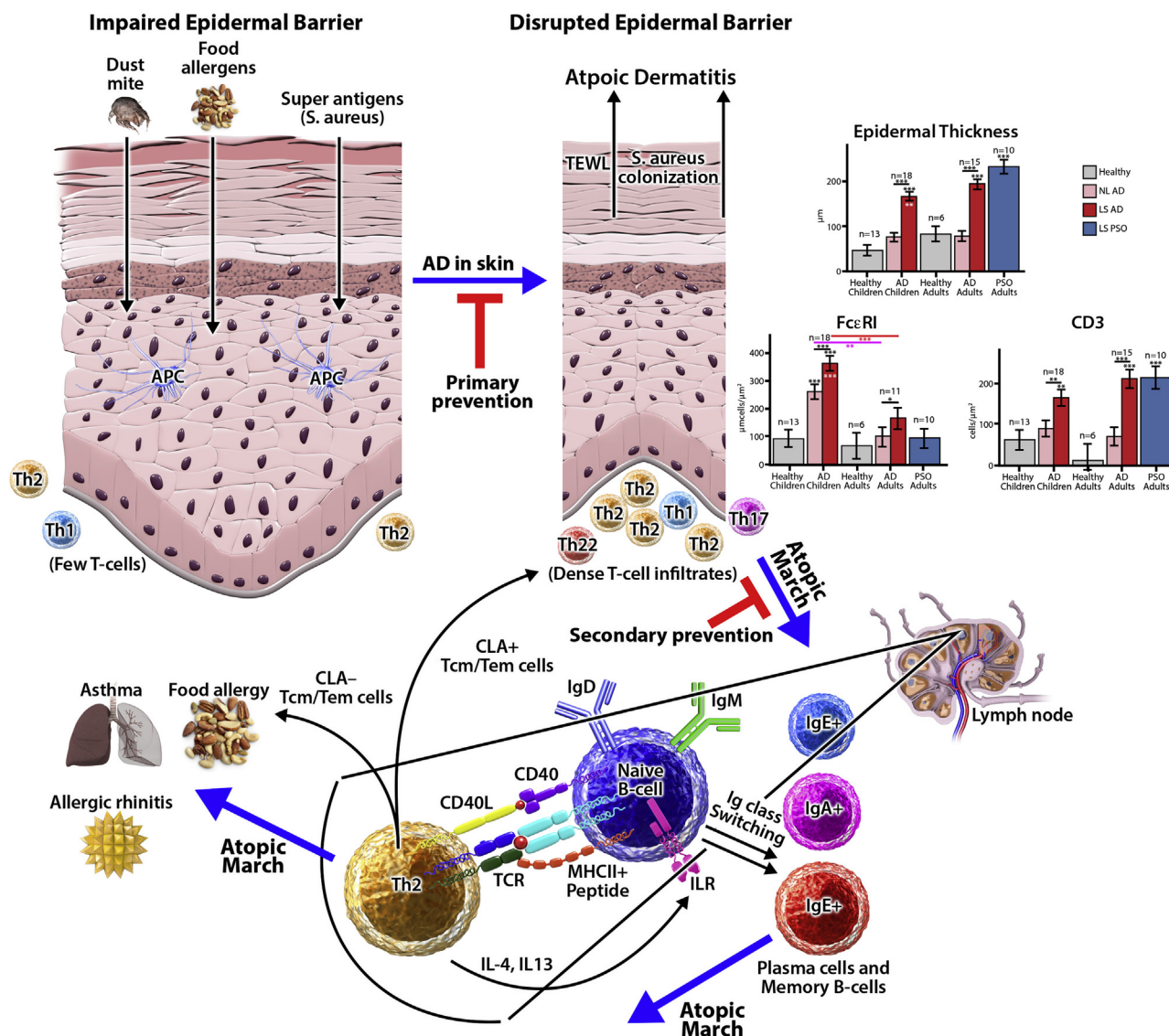


FIG 3. Prevention of AD and the atopic march. Early antigen penetration occurs through an impaired epidermal barrier in high-risk infants. Thus primary prevention to inhibit AD development should focus on barrier-targeted approaches. Should primary prevention fail, overt AD ensues, including increased TEWL, *S aureus* colonization, disrupted epidermal barrier, and dense T-cell skin infiltration. Hyperplastic barrier, excessive CD3⁺ T-cell infiltration, and increased FcεRI expression are all seen in lesional and nonlesional pediatric AD skin (data adapted from Esaki et al⁶⁴ with permission). These full-blown immune and barrier changes subsequently trigger B-cell IgE skewing, T-cell migration, and promotion of the atopic march, including FA, allergic rhinitis, and asthma. ILR, Interleukin receptor; LS, lesional; NL, nonlesional; PSO, psoriasis; TCR, T-cell receptor.

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.⁶⁴

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.^{153,154}

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,¹⁵⁵⁻¹⁵⁷ was significantly higher among the systemic/CLA⁻ memory cells of the youngest cohort, supporting early induction of noncutaneous atopic disorders.¹⁵⁴

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,¹⁵⁸⁻¹⁶¹ 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.¹⁶² These observations indicate that early AD has a different phenotype in blood and skin;

although only T_H2 cells are expanded in the circulation,^{153,163} multiple cytokine axes are activated in skin lesions.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.¹⁶² Thus the atopic march begins with T_H2 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 is imminent when the skin manifestations are already evident).¹⁶⁴ These findings highlight the need for early primary intervention before skin manifestations begin, as well as secondary immune manipulations once the cutaneous phenotype is already evident.

Saunders et al¹⁶⁵ showed that although ILCs prime dermatitis independently of adaptive immunity, the latter is required for the subsequent development of systemic allergies. These data suggest that although primary cutaneous manifestations could be prevented theoretically by innate manipulations, such as skin barrier optimization, secondary prevention of the march will probably require adaptive immune maneuverings.

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.^{166–168} Fig 3⁶⁴ 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.^{52,169–171} Use of moisturizers in premature newborns decreases TEWL, dermatitis severity, and bacterial colonization.^{172–174} An initial small study suggested that petrolatum can be used for primary AD prevention.¹⁷⁵ Recent cornerstone prospective studies showed that moisturizers significantly reduce rates of AD development. In the first open-label uncontrolled pilot study, Simpson et al¹⁷⁶ 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.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 Japan¹⁷⁸ 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.

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.¹⁷⁹ It was shown that petrolatum induces significant upregulation of key AMPs (eg, S100A7/A8/A9/A12, lipocalin 2, elafin/peptidase inhibitor 3, CCL20, and cathelicidin/LL-37) and innate genes and improves expression of epidermal differentiation markers (FLG and loricrin).⁵² It also reduces T-cell and DC infiltrates only among patients with AD.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.^{180,181} Dietary allergen avoidance during pregnancy or lactation in high-risk mothers is not recommended,¹⁸² and the role of other factors (eg, vaccinations, allergen avoidance, and breast-feeding) in preventing AD is still controversial.^{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.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.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.¹⁸⁶ Results showed increased rates of FA and allergic rhinitis in infants with higher AD severity at baseline.

A slightly nonsignificant increase of asthma was observed among the pimecrolimus group, probably secondary to more severe baseline AD.¹⁸⁷ 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.¹⁸⁸ Dupilumab, an IL-4 receptor mAb, has shown efficacy in the treatment of asthma and AD.¹⁸⁹ 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.^{125,190,191} As discussed above, the epithelium-derived cytokines TSLP, IL-33, and IL-25 promote T_H2 responses and are involved in early AD initiation and instigation of other allergic disorders. Thus early blockade of the T_H2 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 modulators on changing the course of the atopic march in children with severe AD.

What do we know?

- Infants with lower skin barrier function have higher risk of developing AD (high risk group).
- Intervention in a high-risk group early in infancy by applying emollients, that may improve barrier function, can reduce risk of developing AD.
- In new onset AD during childhood, T_H2 activation and expansion can be demonstrated in blood and skin lesions.
- There is co-incident IgE isotope switching in immature B cells.
- There is an established effect of T_H2-associated cytokines on promoting IgE class switching.

What is still unknown?

- Particularly in infants with normal filaggrin status, the precise cause(s) of lower skin barrier function are not known.
- The mechanism by which emollient application reduces AD development is not known with certainty.
- The factors that drive early/excess T_H2 activation at initiation of AD are not known.
- Whether the atopic march can be modified by immune intervention once overt AD has developed is not known.

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