



The genetics of the skin barrier in eczema and other allergic disorders

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Purpose of review

We summarize current knowledge on the genetic determinants of skin barrier deficiency in relation to eczema and disease progression to other allergic manifestations.

Recent findings

There is increasing evidence that impairment of epidermal barrier function is not only a risk factor for the development of eczema but also for disease progression to allergic airway disease and food allergy. Support comes from recent association studies linking genetic variants in epidermal genes with eczema and food allergy, from monogenic diseases with severe skin barrier defects which display multiple allergic manifestations, and from mouse models providing a mechanism from skin inflammation to allergic reactions in the lung and intestine.

Summary

The key role of the skin barrier defect in the development of eczema and eczema-associated allergic diseases may have important implications for prevention and treatment strategies. Initial clinical trials with moisturizing creams revealed promising results for the prevention of eczema in early infancy. Their long-term effects will be critical to demonstrate the potential benefit of barrier repair therapy in allergic disease prevention.

Keywords

atopic march, barrier repair therapy, dermatitis, epidermal barrier, food allergy

INTRODUCTION

The skin constitutes the barrier between the organism and its environment protecting against a variety of external hazards, such as mechanical stress, chemical insults, and ultraviolet light. In addition, the skin maintains internal homeostasis by regulating hydration and temperature, it exerts endocrine functions and plays an active role in the immune defence against invading pathogens.

Eczema has a complex etiology with genetic and environmental factors influencing disease risk. It usually develops in infancy and is characterized by chronically relapsing inflammatory skin lesions, severe itch and aberrant immune responses against environmental allergens (atopy). A defective skin barrier is a hallmark of eczema (atopic dermatitis), manifesting clinically as marked dryness, sensitivity to physical/chemical irritation, susceptibility to abnormal bacterial colonization, and increased sensitivity to bacterial and viral infections [1].

Although previous research focused on immunological dysfunction as a causative mechanism and common denominator with other allergic disorders such as asthma, allergic rhinitis, and food

allergy, recent genetic and functional studies, particularly on the epidermal barrier protein filaggrin, moved the limelight onto the skin barrier in the etiology of eczema [2].

The epidermis is a stratified squamous epithelium and the outermost layer of the skin. Skin homeostasis requires a strict balance between proliferation of keratinocytes in the basal layer of the epidermis, differentiation on their way through the suprabasal layers and desquamation of terminally differentiated, dead keratinocytes (corneocytes) on the surface of the cornified layer. Epidermal

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Curr Opin Allergy Clin Immunol 2015, 15:000–000

DOI:10.1097/ACI.0000000000000194

KEY POINTS

- The skin barrier defect plays a key role in the development of eczema and in disease progression to other allergic disorders such as asthma and food allergy.
- Mouse models suggest a mechanism from the impaired epidermal barrier to asthma and food allergy via a TSLP- and IgE-dependent pathway.
- Protection and recovery of the skin barrier in early infancy could be a promising approach to prevent eczema and to reduce the prevalence of eczema-associated allergic diseases.

differentiation involves profound cellular changes including the formation and degradation of specific cell structures, of which desmosomes, the keratin intermediate filaments, the cornified cell envelope, and the lipid envelope are most important for the physico-chemical resistance of the skin.

One important epidermal barrier protein is filaggrin (FLG) [2]. It binds to keratin intermediate filaments and causes their aggregation into densely packed bundles [3]. Moreover, it is linked to the cornified cell envelope (CE), a physically resistant structure that replaces the cell membrane in terminally differentiating keratinocytes. The CE is assembled by cross-linking of its precursor proteins, mainly involucrin, loricrin, and small proline-rich proteins [4]. Additionally, lipids secreted as lamellar bodies to the extracellular space are covalently bound on the outside of the CE [5]. Terminal differentiation of the epidermis culminates in the formation of the cornified layer, in which flattened dead corneocytes consist of a highly cross-linked protein matrix surrounded by a hydrophobic lipid bilayer [6]. Although these structures provide the main permeability barrier, their degradation also contributes to the barrier function of the skin. The tightly regulated proteolysis of desmosomes is essential for a controlled desquamation process. In addition, degradation products of filaggrin serve as natural moisturizing factors (NMFs) [7] that are essential for hydration of the skin and protect from increased transepidermal water loss (TEWL). Finally, NMFs maintain skin pH which is important for an intact microflora and the antimicrobial barrier.

FILAGGRIN DEFICIENCY IN ECZEMA

Loss-of-function mutations in the filaggrin gene (*FLG*) are the archetypical example of a genetically determined skin barrier defect as a primary cause of eczema. *FLG* deficiency results in abnormal structure

and physiology of the epidermis, increased TEWL, and dry skin [8–11]. *FLG* mutations increase the eczema risk three-fold and predispose to early-onset persistent eczema and subsequent allergic sensitization [12,13]. Over 250 mutations have been reported to date, revealing a high level of allelic heterogeneity within and across different populations [14^{***}]. Interestingly, prevalent *FLG* mutations (>1% allele frequency) occur in all populations studied, suggesting an evolutionary advantage for a mildly leaky skin barrier of modern humans. A plausible hypothesis suggested that epicutaneous penetration of small amounts of microbial pathogens promoted natural vaccination in the preantibiotic era [15]. Another proposed a benefit for *FLG* mutation carriers because of enhanced sun-induced vitamin D3 synthesis in populations with less sun exposure, because degradation of filaggrin produces the main endogenous ultraviolet-B filter trans-urocanic acid. The latter hypothesis is supported by the observation of a higher mutation frequency in Northern European populations and increased 25-OH vitamin D3 serum levels in mutation carriers [16^{*},17].

Other factors may influence skin barrier function through decreased *FLG* expression. Variable numbers of *FLG* intragenic tandem repeats encoding 10–12 posttranslationally generated filaggrin monomers have been reported [18]. Lower repeat numbers were associated with dry skin and increased eczema risk in a dose-dependent manner [9,19,20].

Apart from genetic variability, epigenetic changes such as DNA methylation or histone modifications may down-regulate *FLG* expression. Although a small study [21] on buccal mucosa did not reveal a correlation between promoter methylation and *FLG* expression levels, another study [22] reported an association between increased methylation of an intronic CpG site and eczema risk in *FLG* mutation carriers. This study, however, analyzed a small sample, lacked *FLG* expression data, and examined methylation status in leukocytes in which *FLG* is not expressed.

Recently, maternal effects of the *FLG* mutations on the child were analyzed in 1200 nuclear families with eczema. This study [14^{***}] revealed a 50% increased eczema risk in children of mothers carrying an *FLG* mutation. Interestingly, the effect was independent of transmission of *FLG* mutations to the offspring and was observed only in mothers with allergic sensitization. The data suggest that *FLG* deficiency in the mother might lead to systemic immune changes that are transmitted to the child via the ‘in-utero’ environment. The proposed hypothesis is supported by animal studies showing that the immune status of pregnant mothers

influences asthma susceptibility in the offspring [23[¶]]. In addition, epidemiological human studies have demonstrated that exposure to farm environment during pregnancy has a strong protective effect on multiple allergic diseases in the child [24].

SKIN BARRIER GENES IN ASSOCIATION STUDIES ON ECZEMA

Many proteins essential for the differentiation of the epidermis are encoded by genes within the epidermal differentiation complex (EDC) [25], a gene complex on chromosome 1q21.3. As *FLG* is located within the EDC, genome-wide association studies (GWAS) [26–28] on eczema identified this locus with high significance. After adjusting for the *FLG* mutations, a single GWAS reported a residual effect near the hornerin gene (*HRNR*) [28], suggesting that additional risk variants exist in that region. *HRNR* shares many features with *FLG*, such as the structural organization including internal tandem repeats, the expression pattern in the epidermis, and the involvement in the CE [29]. Reduced levels of hornerin were found in affected and unaffected skin of eczema patients [30]. Similarly, reduced skin expression was observed for the filaggrin-2 gene (*FLG2*) that belongs to the same gene family. For *FLG2*, genetic association results with eczema were conflicting [31,32]. Another EDC gene associated with eczema encodes the small proline-rich protein 3 [32]. Members of the small proline-rich protein family serve as highly flexible, cross-bridging spacers in the cell envelope and determine its tissue-specific, physical properties.

Apart from the EDC, noncoding variants in the gene encoding the laminin alpha-3 subunit (*LAMA3*) involved in linking basal keratinocytes with the basement membrane were recently associated with eczema [33]. *LAMA3* loss-of-function mutations cause junctional epidermolysis bullosa that is characterized by mechanically induced skin blistering and fragility. In addition, variants in a component of the extracellular matrix of the epidermis (*COL6A5/COL29A1*) were associated with eczema and allergic sensitization [34]. Replication, however, failed in several populations [35]. A recent study [36] identified a missense mutation in the human gene *TMEM79* to be associated with eczema, suggesting a genetically determined defect of the lipid barrier. In knockout mice, lack of *Tmem79* (*matrin*) impairs the extracellular secretion of lamellar body contents, including lipids, proteases, and its inhibitors in the CE. As a consequence, mice develop spontaneous dermatitis. Overall, independent replications and further functional evaluations will be required to confirm and

understand the role of these barrier genes in eczema etiology.

In the last decade, GWAS have been used to scan the genome for common variants influencing disease risk. The latest GWAS meta-analysis for eczema, including more than 100 000 individuals, has recently increased the number of known GWAS loci to 32 (under review). This study revealed an enrichment of eczema risk variants in open-chromatin regions of immune cells pointing to genomic elements involved in transcriptional regulation of the immune response. Overall, GWAS studies point to immunity rather than epidermal barrier as a disease driver, although some genes located on GWAS regions play an important role in the immune response to microbes (*IL1RL1* [37,38], *IL21* [39], *IL22* [40,41]), production of IgE (*IL4*, *IL13* [42]), or in skin inflammation and homeostasis (*STAT3* [43,44]) and can be regarded as part of the immune barrier of the skin. Interestingly, two recent studies [45[¶],46^{¶¶}] found *IL1RL1*, *IL22*, and *STAT3* to be dysregulated in the skin of eczema patients supporting their role in the local immune response.

One epidermal barrier gene suggested by GWAS is *OVOL1* on 11q13.1, which is upregulated during keratinocyte differentiation and plays a role in skin-barrier development [47,48]. Moreover, a recent study [49[¶]] demonstrated that *OVOL1* inhibits the proliferative state of keratinocytes in the basal layer and promotes terminal differentiation.

In summary, there is a discrepancy between the underrepresentation of obvious barrier genes in GWAS regions and recent findings on the importance of the skin barrier in eczema. The causal genes in most GWAS regions are, however, currently unknown and fine-mapping and functional studies are required to face this challenge. Additionally, GWAS focus only on common variants (>5% allele frequency) and the loci identified so far explain only a small proportion of the heritability. Future studies targeting common and rare variants in larger populations may reveal additional skin barrier genes influencing eczema risk.

MONOGENIC DISEASES – A LINK BETWEEN SKIN BARRIER DEFECTS AND ALLERGIC MANIFESTATIONS

Although the primary skin barrier defect in eczema is usually less pronounced, monogenic skin disorders may present a severely impaired skin barrier. Interestingly, these genodermatoses also provide a link to noncutaneous allergic manifestations. We highlight three monogenic diseases that are caused by mutations in genes involved in cornification, display a severe barrier defect including dermatitis,

Table 1. Monogenic defects of skin barrier associated with allergic diseases

	SAM syndrome (MIM 125670)	Peeling skin syndrome type B (MIM 270300)	Netherton syndrome (MIM 256500)
Gene	<i>DSG1</i>	<i>CDSN</i>	<i>SPINK5</i>
Inheritance	Recessive	Recessive	Recessive
Protein	Desmoglein 1	Corneodesmosin	Lympho-epithelial Kazal-type-related inhibitor (LEKTI)
Function	Structural component of desmosome, epidermal integrity	Extracellular protein; associates to desmosome; cell–cell cohesion within upper epidermis and stratum corneum	Protease inhibitor, regulation of desquamation
Skin-specific expression	+	+	+/-
Skin symptoms	Congenital erythroderma, severe dermatitis, scaling, erosions	Ichthyosiform erythroderma, scaling, exfoliation, pruritus, barrier defect	Congenital ichthyosiform erythroderma, scaling and eczema-like lesions, pruritus
Elevated serum IgE	+	+	+
Other allergic symptoms	Severe food allergy, allergic sensitization	Food allergy, asthma, eosinophilia	Food allergy, asthma, rhinitis, angioedema
Complications	Failure to thrive, metabolic wasting, skin and respiratory infections, developmental delay	Failure to thrive, skin infections	Risk of neonatal death, failure to thrive, growth retardation, recurrent infections, dehydration
Mouse knockout	<i>Dsg1a</i> and <i>Dsg1b</i> (no skin phenotype)	Neonatal lethal, skin barrier defect, stratum corneum detachment	Neonatal lethal, skin barrier defect, stratum corneum detachment
References	[50,51 [■]]	[52–54]	[55,56]

and, additionally, multiple allergic manifestations apart from the skin phenotype (Table 1) [50,51[■], 52–56].

Heterozygous loss-of-function mutations in the gene encoding the desmosomal protein desmoglein 1 (*DSG1*) cause thickening of the skin on palms and soles (palmoplantar keratoderma I, MIM 148700) [57]. Two recent studies [50,51[■]] reported that homozygous *DSG1* mutations cause ‘severe dermatitis, multiple allergies, and metabolic wasting’ (SAM syndrome; MIM 125670). In skin of affected individuals, lack of *DSG1* expression leads to loss of adhesion between keratinocytes and spontaneous detachment of the epidermis. Clinical symptoms include severe dermatitis, palmoplantar keratoderma, elevated total and specific IgE levels, and severe food allergies.

Peeling skin syndrome type B (also called generalized peeling skin disease; MIM 270300) is caused by homozygous mutations in the corneodesmosin gene (*CDSN*), which encodes an extracellular protein associated with desmosomes and corneodesmosomes in the skin [52]. Corneodesmosin-deficient skin showed reduced adhesion between corneocytes and a loose cornified layer leading to scaling, reddening, and spontaneous peeling of the skin and severe pruritus. Additionally, affected individuals present multiple allergic manifestations

including high levels of total IgE severe pruritus, food allergies, angioedema, and asthma.

Netherton syndrome (MIM 256500) manifests neonatally with severe skin inflammation, scaling, and itch, and can lead to life-threatening complications [55]. Patients suffer from constant allergic manifestations including elevated IgE levels, asthma, allergic rhinitis, food allergy, angioedema, and eosinophilia. Netherton syndrome is caused by recessive mutations in serine protease inhibitor of kazal type 5 (*SPINK5*) encoding LEKTI-1 (lympho-epithelial kazal-type-related inhibitor type 5), which is a protease inhibitor essential for skin homeostasis. Lack of LEKTI-1 results in enhanced activities of epidermal proteases promoting desquamation of corneocytes.

Deciphering the pathogenesis of the above disorders substantiates the concept that a primary epidermal defect can predispose to allergic manifestation not only in skin. Animal models with targeted defects in *Cdsn* and *Spink5* support these results (Table 1) [53,54,56]. Notably, a defect of the skin barrier may be due to disturbed formation of epidermal structures or of their aberrant degradation, emphasizing the importance of a tightly regulated skin homeostasis. A number of additional monogenic disorders of cornification have been identified [58], and the potential involvement of

the disease-causing genes in allergic disorders remains to be investigated.

EPIDERMAL BARRIER DYSFUNCTION AND THE ATOPIC MARCH

The atopic march describes the sequential development of allergic conditions frequently observed in children with IgE-antibody responses against common environmental allergens (atopy) [59,60]. Although various patterns of the atopic march have been discussed, eczema is the first allergic manifestation in more than 60% of children with multiple allergies [61]. In addition, about 20–30% of infants with eczema develop later asthma and these children suffer from severe and persistent allergic disease manifestations. Consistently with the epidemiological results, there is increasing evidence from genetic studies that eczema plays a key role in the atopic march and that an impaired skin barrier promotes disease progression to allergic airway disease and food allergy.

Mutations in *FLG* were the first genetic risk factors to be associated with disease progression from eczema to asthma [12,62,63]. Notably, asthma risk was restricted to individuals with prior eczema and increased further in atopic individuals, pointing to a role for epicutaneous sensitization in the atopic march. *FLG* mutations also increase the risk of allergic rhinitis, although it is not clear if this effect is independent of previous eczema [12].

Further support for a central role of eczema in the atopic march comes from a recent GWAS on children with infantile eczema and childhood asthma. The strongest risk in that study was provided by the *FLG* locus. In addition, there was a significant overrepresentation of eczema loci among the identified susceptibility loci, suggesting that genes involved in eczema rather than in asthma are the main driver of the atopic march (under review).

Several mouse models support a disease mechanism leading from impairment of the epidermal barrier and eczema to enhanced epicutaneous allergen penetration and subsequent asthma development via an IgE-dependent pathway (Table 2) [64,65,66,67–69]. In Balb/c mice, which are prone to developing allergic responses, allergen exposure through irritated skin induced localized dermatitis, systemic specific IgE production, and airway hyper-responsiveness upon challenge with aerosolized antigen [64]. Likewise, skin exposure to inhalant allergens induced nasal allergic responses upon intranasal antigen challenge [70].

The flaky tail mouse revealed a path from genetic epidermal defects to dermatitis and

Table 2. Selected mouse models relevant for skin barrier function and the atopic march

Strain	Skin challenge	Epicutaneous sensitization	Dermatitis	Other allergies	Conclusion	Reference
Balb/c	Shaved skin + OVA	Yes	Induced	Asthma	Epicutaneous sensitization elicits skin inflammation, systemic immune responses and asthma-like phenotype upon i.n. challenge	[64]
Balb/c	Tape stripping + OVA	Yes	Induced	Asthma	Skin barrier disruption and exposure to antigen induce dermatitis, epicutaneous sensitization and asthma upon i.n. challenge	[65]
Balb/c <i>Tslp^{flap-/-}</i> (Tslp ablation in keratinocytes)		↓	↓	↓ Asthma	Ablation of TSLP in keratinocytes reduces dermatitis, sensitization and asthma	
Balb/c	Tape stripping + OVA + MC903	↑	↑	↑ Asthma	Upregulation of TSLP in skin by topical treatment with MC903 aggravates Th2 response and asthma	

Table 2 (Continued)

Strain	Skin challenge	Epicutaneous sensitization	Dermatitis	Other allergies	Conclusion	Reference
Balb/c	Topical treatment with MC903 (AD-like lesion) or Tape stripping + OVA	Yes	Yes	Food allergy	Sensitization through a disrupted skin barrier induces basophil-dependent food allergy upon i.g. challenge	[66 ^{***}]
Balb/c <i>Igh-7</i> ^{-/-} (IgE deficient)		↓	↓	↓ Food allergy	Model is dependent on IgE	
Balb/c <i>Tslpr</i> ^{-/-} (TSLPR deficient)		↓	↓	↓ Food allergy	Model is dependent on TSLP-TSLPR interactions	
<i>Flg</i> ^{fl/h} <i>Tmem79</i> ^{ma/ma} (Double <i>Flg</i> <i>Tmem79</i> mutant)	No	N.a.	Spontaneous	N.a.	FLG deficiency: no spontaneous dermatitis, dry, scaly, fragile skin, abnormal keratin filament aggregation, defective skin barrier, no asthma upon i.n. challenge Tmem79 deficiency: spontaneous dermatitis, impaired lamellar granule secretion, disorganized lipid morphology of cornified envelope, fragile skin, defective skin barrier, enhanced epicutaneous sensitization	[36,67]
<i>C57BL/6J Flg</i> ^{fl/h} (p.N1768Tfs*154)	No	N.a.	No	N.a.		[36,67]
	Clipped hair + HDM	No	No	N.a.		[36]
	Shaved skin + OVA	↑	Induced	No asthma		[68]
<i>Flg</i> ^{-/-} (<i>Flg</i> knockout)	Irritant, hapten or OVA on ear	↑	Induced	N.a.		[69]
<i>C57BL/6J Tmem79</i> ^{ma/ma} (p.Y280X)	No	N.a.	Spontaneous	N.a.		[36,67]
	Clipped hair + HDM	↑	Increased by treatment	N.a.		[36]

↓, Reduced compared with control group; ↑, increased compared with control group; asthma, asthma-like phenotype; CPE, crude peanut extract; food allergy, food allergy-like phenotype; HDM, house dust mite; i.g., intragastric; i.n., intranasal; MC903, calcipotriol (vitamin D3 analog); N.a., not tested; OVA, ovalbumin.

epicutaneous sensitization, and has been widely used as a model for skin barrier deficiency because of loss-of-function mutations in *FLG*. Two recent studies [36,37], however, demonstrated that these mice carry loss-of-function mutations in two different barrier genes, *Flg* and *Tmem79*. Surprisingly, filaggrin-deficient mice (*Flg^{fl/fl}*) shared the impaired barrier function and enhanced epicutaneous allergen priming with the double mutant flaky tail mouse (*Flg^{fl/fl} Tmem79^{ma/ma}*) but did not develop spontaneous dermatitis [68]. These observations were confirmed in an independent study [69] analyzing a *FLG* knockout mouse (*Flg^{-/-}*). In contrast, the matted mouse (*Tmem79^{ma/ma}*) carrying a loss-of-function mutation in *Tmem79/Matt* spontaneously developed dermatitis pointing to the important role of the lipid barrier [67]. *Tmem79*-deficiency resulted in impaired lamellar granule secretion, disorganized lipid morphology of the cornified envelope, fragile skin, and a defective skin barrier leading to enhanced epicutaneous sensitization. Finally, epicutaneous sensitization in the *Flg^{fl/fl}* mouse did not lead to increased allergic response in the airways upon intranasal antigen challenge [68]. This lack of response may be because of the genetic background of the C57BL/6J strain which is known to be less immunoreactive than the commonly used Balb/c.

Recently, a mouse model provided a mechanistic link between the epidermal barrier defect and asthma. In this study, specific ablation of thymic stromal lymphopoietin (TSLP) in keratinocytes strongly reduced sensitization through mechanically disrupted skin and subsequent asthma development. Inversely, upregulation of TSLP in the skin resulted in increased sensitization and asthma [65]. TSLP is a cytokine produced by barrier surface epithelial cells in skin, lung, and gut, acting on different immune cells to promote Th2 responses [71]. Interestingly, increased levels of TSLP have been reported in serum and skin of eczema patients reinforcing its role in the disease [72,73].

Although the mechanism leading from the skin barrier defect and eczema to allergic airway disease becomes more and more evident, the role of food allergy in the atopic march still needs to be determined. Until recently, oral sensitization to foods was thought to be critical and avoidance of allergenic foods in early infancy was usually recommended as a preventive measure. Studies [74[■],75–77] demonstrating adverse effects of early food avoidance and a protective effect of oral allergen tolerance, however, changed this view. Association studies on *FLG* loss-of-function mutations supported the critical role of the epidermal barrier also for sensitization to food allergens and for the development of food allergies. Interestingly, several studies demonstrated that the effect

on food allergy was restricted to children and adults with a history of eczema [78[■]], comparable with the *FLG* effect on asthma. Likewise, *FLG* mutations did not affect food sensitization in the absence of eczema, neither in early infancy nor in adulthood [79[■],80], indicating that further breakdown of the barrier because of inflammation is critical for epicutaneous sensitization and subsequent food allergy. A single study [81] reported an *FLG* effect on peanut allergy independent of the eczema status. An interaction between early exposure to peanut dust and *FLG* mutations on peanut sensitization at later age pointed to a strong environmental component in peanut allergy [82[■]], likely due to the filaggrin-deficient barrier. This is in line with previous epidemiological studies demonstrating an increased risk of peanut allergy after topical application of peanut oil to inflamed skin [83]. Further evidence for a link between the defective epidermal barrier and food allergy comes from mouse models. Epicutaneous sensitization to ovalbumin (OVA) or peanut allergen through tape-stripped skin promoted IgE-mediated anaphylaxis and mast cell degranulation in the intestine upon oral antigen challenge [84]. Another study [66[■]] demonstrated that TSLP-elicited basophils in the skin promoted local inflammation and the development of IgE-mediated intestinal food allergy in response to oral antigen exposure. Finally, in a mouse model, OVA-induced food allergy was associated with a worsening of house dust mite-induced asthma symptoms, providing a link between food allergy and asthma [85].

RECOVERY OF THE SKIN BARRIER – A KEY FOR THE PREVENTION OF ECZEMA AND ALLERGIES?

Considering the importance of the skin barrier defect in the development of eczema and other allergic diseases, a barrier repair therapy in early infancy is a promising approach to prevent or ameliorate eczema. Two recent clinical studies aimed to prevent eczema and allergic sensitization by early protection of the barrier with skin emollient therapy. Daily application of an emulsion-type moisturizer in the first 32 weeks of life increased stratum corneum hydration at week 12 and reduced the cumulative incidence of eczema at week 32 by 32% [86[■]]. In the second study [87[■]], daily full-body emollient therapy started within 3 weeks after birth and reduced the incidence of eczema at 6 months by 50%. Although both studies relied on fewer than 120 individuals, the results are encouraging. They demonstrate that barrier repair therapy from birth might represent an effective, well tolerated, and low-cost approach for the prevention of

eczema. If confirmed in larger trials and if long-term effects can be established, protection of the skin barrier could be a key to reducing the prevalence of eczema-associated allergic diseases.

A different approach aimed to correct filaggrin deficiency with a functional filaggrin monomer linked to a cell-penetrating peptide [88^{***}]. The filaggrin construct was successfully delivered to the cytoplasm of human keratinocytes *in vitro*, and restoration of the stratum corneum by processing to filaggrin monomers was demonstrated in flaky tail mice. Although this study established an innovative system for protein replacement in the epidermis, it should be noted that filaggrin delivery was unspecific and not restricted to the upper layers of the epidermis. Although no side-effects or immunological responses were observed in mice due to atypical localization of filaggrin, humans might respond differently. Provided that the safety of this system can be demonstrated in humans, the approach may be useful to correct filaggrin deficiency and other more severe genodermatoses.

The logical next step is to target barrier-restoration therapies to individuals with a high risk of eczema and other associated allergies, which may benefit most. Such preventive treatment should be implemented at an early age before eczema and allergic sensitization have occurred. A recent study [89^{*}] showed that elevated TEWL at 2 days of age together with a parental history of atopy is strongly predictive of eczema at 1 year. Thus, early measuring of TEWL can be used as a noninvasive and effective tool for prediction of eczema and paves the road for designing intervention studies focusing on high-risk individuals.

CONCLUSION

Impairment of the skin barrier is a key event in the development of eczema. Moreover, it can be the first step of a pathway leading from skin inflammation and epicutaneous sensitization to allergic manifestations in other organs such as lung or intestine. Novel findings on the role of filaggrin in food allergy and on TSLP- and IgE-dependent mechanisms involved in allergic disease progression further support the concept of the atopic march. The protection and recovery of the skin barrier in early infancy might represent an effective, well tolerated, and low-cost approach for the prevention and treatment of eczema. In the long term, it might furthermore reduce the prevalence of eczema-associated allergic diseases.

Acknowledgements

None.

Financial support or sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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