La malattia atopica: un concetto in evoluzione

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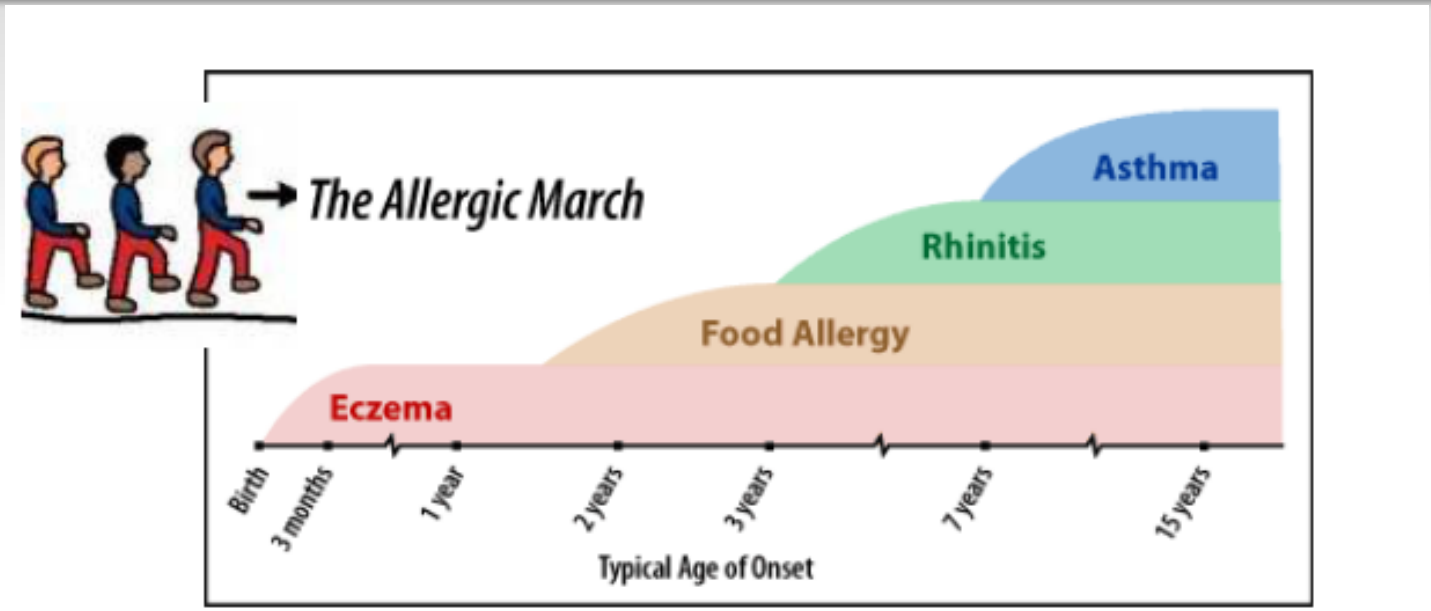
First manifestation of atopy: frequently atopic dermatitis (AD), followed by food allergy, allergic rhinitis and allergic asthma

The term "atopic march" (or "allergic march") describes this temporal relationship in the natural history of atopic disease



H. Hongwei et al., "The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines", Immunol Rev 2017;278:116

T. Zheng et al., "The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma", Allergy, Asthma & Immunol Res 2011, 3:67

Studies Support a Significant Association Between AD and Subsequent Atopic Diseases in Children and Adults

- **Study in >1000 infants with AD (US population-based study)[1]**
- **Approximately 11% developed asthma**
- **37% had one or more atopic comorbidities**
- **Development of allergic rhinitis and food allergy correlated with baseline severity of AD**

- **Study in 7157 children with AD (PEER=Pediatric Eczema Elective Registry observational study)[2]**
- At enrollment:
  - 47%: asthma, and wheezing
  - 63%: seasonal allergies
  - 24%: food allergy

- **Study in >27,000 adults with AD (US population-based study)[3]**

Atopic condition	Prevalence[2]		*P* value
	Adults with AD	Adults without AD	
Lifetime asthma (%)	21.1	11.7	<0.001
Asthma attack within previous year (%)	40.8	31.6	<0.001
Current allergic rhinitis (%)	15.7	6.9	<0.001

Data suggest that the atopic march progresses past childhood

1. L.Schneider L et al., Study of the atopic march: development of atopic comorbidities. Pediatr Dermatol 2016;33:388
2. JC Margolis et al., Persistence of mild to moderate atopic dermatitis. JAMA Dermatol 2014;150:593
3. Silverberg JI et al., Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013;132:1132

1. ENVIRONMENTAL FACTORS in atopic disease development

Sensitization to Environmental Factors

- Exposure to environmental factors (e.g. allergens) leading to:
  - Type 2 cell activation
  - IgE production
  - Mast cell proliferation
  - Eosinophil activation

Over the last century, there has been a rapid rise in atopic disease incidence, particularly in more industrialized countries

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proposal of the "hygiene hypotesis"

↓

early infectious or microbial exposures may play a protective role against the development of atopic disease

↓

Our understanding of how infectious or microbial exposures affect atopic disease risk remains limited, but several studies suggest that these exposures may "tolerize" the immune system and adaptive immune system through effects on both the innate immune system and adaptative immune system

H. Hongwei et al., "The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines", Immunol Rev 2017;278:116

2. Epidermal Barrier Dysfunction
THE GENETIC of atopic disease and the atopic march

Based primarily on twin studies of asthma and atopic dermatitis, the heritability of atopic disease has been estimated to be around 60-75%

Epidermal Barrier Dysfunction

- Genetic alterations in:
  - Epidermal barrier proteins (*FLG*, *LOR*, *IVL*)
  - Antimicrobial peptides (AMPs)
  - Tight junction proteins (*CLDN1*)
- Microbial dysbiosis

Epithelial defects

Inherited defects in epidermal barrier proteins facilitate the interaction of external antigens with skin-resident immune cells, driving local inflammation that can also lead to systemic immune responses

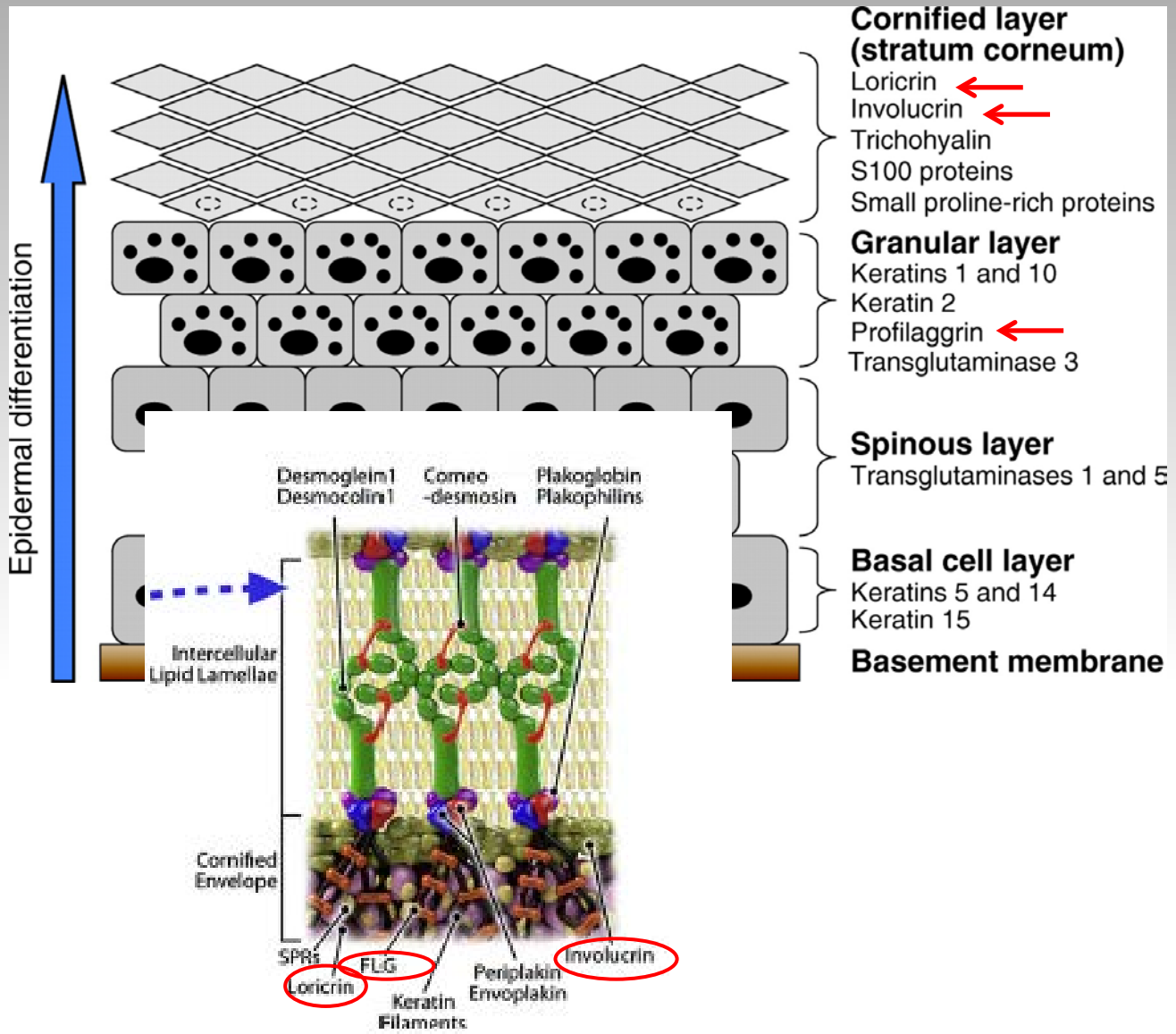
↓

It is now evident that this secondary immunologic activation results in further attenuation of the skin barrier, which further exacerbates inflammation and allergic sensitization to environmental allergens

↓

Maintaining skin barrier function is important for both the effective management of AD and prevention of the development of subsequent allergic disease

G Egawa et al, “Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march” J Allergy Clin Immunol 2016;138:350



Epidermal Barrier Dysfunction

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Sandilands et al, "Filaggrin in the frontline: role in skin barrier function and disease" J Cell Sci 2009;122:1285

G Egawa et al, "Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march" J Allergy Clin Immunol 2016;138:350

Journal of Dermatological Science 76 (2014) 81–89

Invited review article

Classification of inflammatory skin diseases: A proposal based on the disorders of the three-layered defense systems, barrier, innate immunity and acquired immunity

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Epidermal Barrier Dysfunction

- Genetic alterations in:
  - Epidermal barrier proteins (*FLG*, *LOR*, *IVL*)
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4.2.2 *Antimicrobial peptides*

There are numerous AMPs identified in keratinocytes, including human β-defensins (HBD)-1, -2 and -3, cathelicidin (LL-37) and psoriasin (S100A7) [61]. In addition to their antimicrobial effects, they have roles in migration of granulocytes, dendritic cells, and T-lymphocytes and the activation of the innate and acquired immune responses.

The expression of AMPs is downregulated in atopic dermatitis, probably due to the effect of the Th2 cytokines IL-4 and IL-13 [61]. High levels of aberrantly processed forms of cathelicidin peptides contribute to the increased inflammation in the rosacea skin [61]. In psoriasis, as mentioned in the preceding section, cathelicidin self-DNA complexes promote activation of TLR9 on pDCs in the dermis, resulting in enhanced cutaneous inflammation that contributes to its pathogenesis [61].

Tight junctions (TJs) are structures essential to the integrity of the skin barrier
In the skin, they seal adjacent keratinocytes in the stratum granulosum and act as a barrier for water and solutes

Epidermal Barrier Dysfunction

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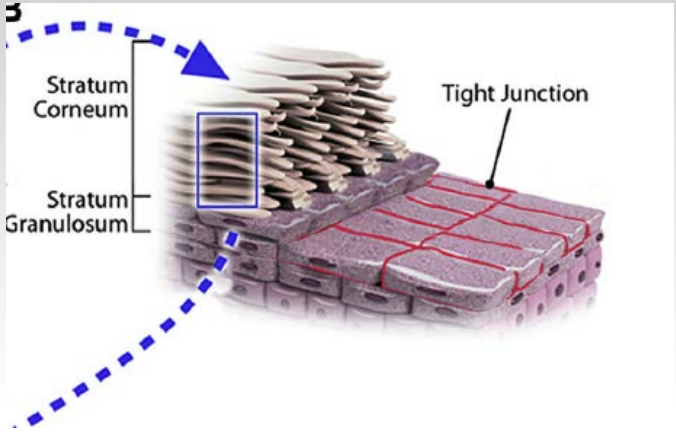

In human subjects **CLDN1** (encoding **claudin1**) expression is reduced in nonlesional skin of patients with **AD** and an association between CLDN1 polymorphism and AD susceptibility has been reported

J Allergy Clin Immunol. 2011 July ; 128(1): 242–246.e5. doi:10.1016/j.jaci.2011.02.014.

Reductions in Claudin-1 May Enhance Susceptibility to HSV-1 Infections in Atopic Dermatitis

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Mark K. Slifka, PhD[c]
Nicholas M. Rafaels, MS[a]
I-Hsin Kuo, MS[a]
Steve N. Georas, MD[b]
Mark Boguniewicz, MD[f]
Tissa Hata, MD[g]
Lynda C. Schneider, MD[h]
Jon M. Hanifin, MD[d]
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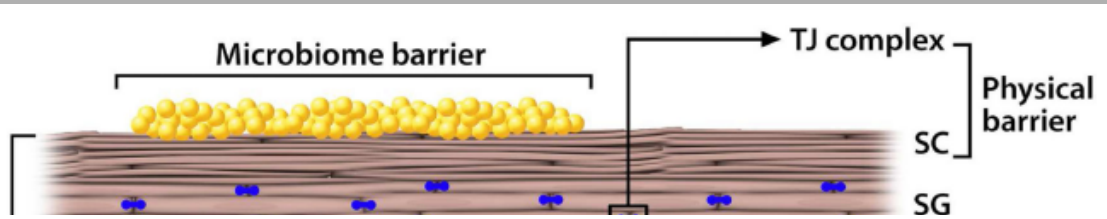
Kathleen C. Barnes, PhD[e]
Donald Y. M. Leung, MD, PhD[f]
Lisa A. Beck, MD[a]

sesses TJs and these structures express claudin-1.[11,12] In this study, we show both mechanistic and genetic results that implicate TJs as a critical barrier structure important in containing the spread of epidermal HSV-1 infections. Defects in TJ compared with the SC may be particularly relevant in viral infections in which the virus enters from a basolateral direction, as is the case with HSV reactivation. Collectively, this work highlights a previously underappreciated role for TJ proteins in cutaneous host defense and may lead to new therapeutic strategies.



Epi
D

- Gene
  - E
    p
    IV
  - Ti
    p
  - A
    p
- Microbial dysbiosis

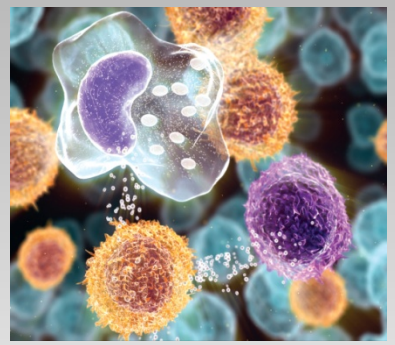
Loss of skin barrier function and increased severity of AD predisposes to microbial colonization and chronic skin inflammation. This is due to increased expression of tissue receptors for *Staphylococcus aureus* that leads to colonization of *S. aureus* in atopic skin (52, 53). Keratinocytes from AD skin have also been found to be deficient in their ability to produce antimicrobial peptides that are needed to control *S. aureus* and viral replication (54,55). Interestingly commensal bacteria also produce antimicrobial peptides capable of controlling *S. aureus* growth (56). *S. aureus* produce high levels of serine proteases that can degrade skin barrier (57). Therefore an overabundance of *S. aureus* in poorly controlled AD can reduce barrier function via multiple mechanistic pathways.

(193) found at the level of the stratum granulosum (SG) provide an additional barrier. Disruption of both physical barriers enables the uptake of allergens, irritants, and microbes by Langerhans cells (LC)/DCs. Keratinocytes produce AMPs as a chemical barrier in response to pathogen colonization/infection. The skin surface is colonized with a diverse array of microorganisms (microbiome barrier), which iregulates local immune responses and inhibits pathologic microbes. Infiltration of a number of cells into the AD skin lesion, including T cells, eosinophils (Eos), DCs, NK cells, and mast cells/basophils. Collectively, these cells constitute the cutaneous immunologic barrier. Pattern recognition receptors (PRRs) regulate the function of all of these barriers (physical, chemical, microbiome, and immunologic). SB, Stratum basale; SG, stratum granulosum; SS, stratum spinosum. This figure is modified from Kuo I, et al. J Allergy Clin Immunol 2013;131:266-78.

D.Y.M. Leung et al, "Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches" J Allergy Clin Immunol 2014;134:769

3. Chronic Immunologic Inflammatory Response

WHAT'S NEW?



Chronic Immunologic Inflammatory Response

- Type 2 responses
  - IL-4, IL-5, IL-13
- Type 1 responses
  - IL-22, IFN-ɣ

Three epitelial cell-derived cytokines: thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33) and interleukin-25 (IL-25) have emerged as potent inducers of type 2 inflammation at barrier site

H. Hongwei et al., "The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines", Immunol Rev 2017;278:116

Chronic Immunologic Inflammatory Response

TSLP promotes Th2 cytokine responses through its actions on mast cells, innate lymphoid cells (ILCs), epithelial cells, macrophages and basophils. Together with IL-1 and tumor necrosis factor, TSLP can costimulate the activation of human mast cells to induce Th2 cytokines

A model of the atopic march in mice in which skin sensitization is induced through intradermal injection of TSLP in the presence of antigen (OVA) was developed

Although TSLP expression was undetectable in normal skin, it was found to be highly expressed in the lesional skin of individuals with AD and in the airways of asthmatics
In eosinophilic esophagitis, a gain-of-function polymorphism in TSLP is associated with disease in pediatric subjects

After skin sensitization, intranasal antigen challenge promoted airway inflammation and oral antigen challenge drove allergic diarrheal disease

H. Hongwei et al., “The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines”, Immunol Rev 2017;278:116

Chronic Immunologic Inflammatory Response

IL-33 drives **eosinophil differentiation** from bone marrow precursors in vitro and stimulate cytokine **production** in **eosinophils** and **mast cells**
It can also promote **basophil activation** and **migration**

The expression of IL-33 in **skin** and **airway epithelium** can be further increased in **AD** and during **airway inflammation** in both humans and mice

Skin-specific overexpression of IL-33 can drive spontaneous dermatitis in mice

H. Hongwei et al., “The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines”, Immunol Rev 2017;278:116

Chronic Immunologic Inflammatory Response

IL-25 is a member of the IL-17 cytokine family that was originally reported to be expressed by Th2-polarized CD4+ T cells

Exposure to allergens, air pollutants and infection with helminths can increase IL-25 expression at mucosal sites. In vitro cultures, allergens and proteases (trypsin and papain) can induce the release of IL-25 by human bronchial epithelial cells

IL-25 expression is elevated in the skin of AD patients; in the skin, IL-25 can inhibit filaggrin expression. Blocking IL-25 in an experimental model of allergic asthma inhibited airway inflammation and hyperresponsiveness

H. Hongwei et al., “The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines”, Immunol Rev 2017;278:116

What is the role of the skin as a site of sensitization in the development of the atopic march?

- the AD tends to precede atopic disease

- even in the absence of AD, children with skin barrier defects are still at a higher risk for asthma than healthy children

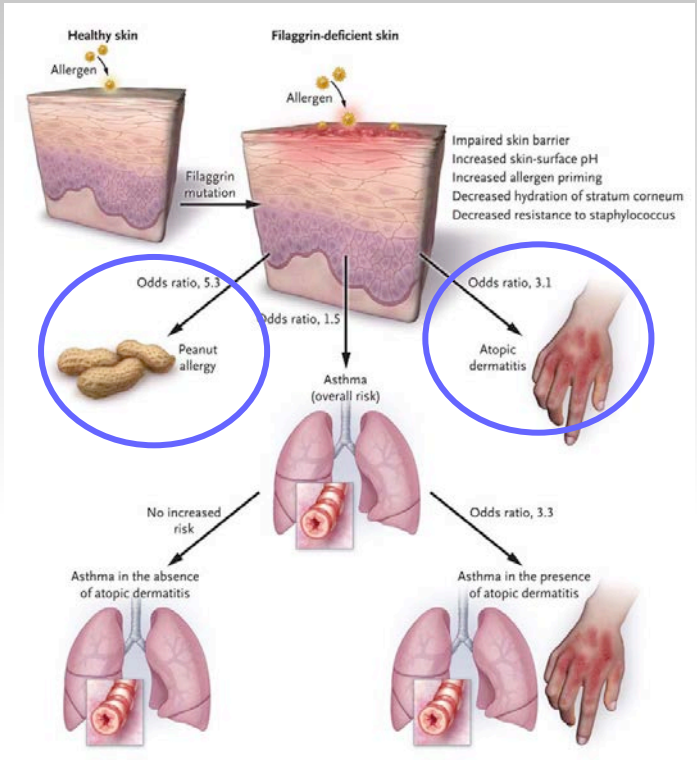
- some occupational exposures that likely occur through the skin, such as exposure to isocyanates (or beryllium), can increase asthma risk

- a case-control study in Japan showed that use of a wheat-containing facial soap was positively correlated with development of food allergy to wheat

- Avon Longitudinal Study of Parents and Children demonstrated that application of peanut oil to inflamed skin was positively associated with the development of peanut food allergies

H. Hongwei et al., “The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines”, Immunol Rev 2017;278:116

Atopic Dermatitis Increases The Effect of Exposure to Peanut Antigen in Dust on Peanut Sensitization and Likely Peanut Allergy



- **Peanut protein in household dust assessed in cohort of highly atopic children (age 3–15 months)**
- **There was an exposure-response relationship between peanut protein levels in household dust and peanut SPT sensitization – and likely allergy**
- **Effect of EPE on peanut SPT sensitization augmented in:**
  - **Children with history of AD**
  - **Children with history of severe AD**
- **Exposure to peanut antigen in dust through impaired skin barrier is a plausible route for peanut sensitization and peanut allergy**

EPE, environmental peanut exposure; SPT, skin prick test.

AD Irvine et al. ”Mechanism of disease: filaggrin mutations associated with skin and allergic disease” N Engl J Med 2011;365:1315
HA Brough et al. ”Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy” J Allergy Clin Immunol 2015;135:164

TAKE HOME MESSAGE…

The concept of the atopic march was developed to describe the progression of atopic disorders from AD in infants to food allergy, allergic rhinitis and asthma later in life

Epidemiological, genetic and experimental studies suggest that skin barrier defects that allow increased exposure and sensitization to allergens may be important factors in the march from allergic skin inflammation to disease at other site

Therapy targeting the maintenance and repair of the epidermal barrier in infants with AD may prevent the subsequent development of subsequent allergic diseases

Skin barrier is also an important source of cytokines, that may initiate and drive type 2 inflammation. The requirements for these epithelial cytokines in both the initiation and maintenance of inflammation make them attractive targets for therapy