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Contribution of an impaired epithelial barrier to the atopic march

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Allergic childhood diseases exhibit a high degree of comorbidity. The concept of the atopic march is based on observations that eczema tends to precede later development of asthma and allergic rhinitis (AR). The causal nature of this progression, however, remains a topic of debate. It has been suggested that the atopic march is initiated through eczema in early childhood and that eczema promotes the development of food and airway allergies by driving systemic sensitization through a compromised epithelial barrier. An alternative hypothesis holds that eczema, food allergy, and airway allergy are independent manifestations of a dysfunctional immune system that predisposes individuals to IgE-mediated allergic reactions in response to environmental stimuli.

Both eczema and asthma are complex diseases with many reported phenotypes. Although eczema is a major risk factor for later airway allergies,^{1,2} only a fraction of children with early eczema develop asthma, and not all asthma cases are preceded by eczema. Nevertheless, accumulating evidence indicates that in a subset of children an impaired skin barrier results in eczema and facilitates cutaneous sensitization, which increases the risk for systemic allergic responses. Although some epithelial barrier defects may be specific to the skin, others likely lead to compromised barriers at other epithelial surfaces, including the gut and the lungs. The skin, specifically the presence of eczema, gives us an easily recognizable window into the underlying faulty epithelial barrier that likely affects the skin, lung, nose, and gut. It is unlikely that eczema causes disease progression or the atopic march; rather, eczema is a symptom that signals underlying epithelial barrier dysfunction that confers risk for disease progression and the atopic march.

Studies have found that allergic diseases are strongly influenced by genetics.³ The importance of skin barrier defects in the development of atopic dermatitis have been convincingly demonstrated in genetic association studies, which have found associations between eczema and genes that code for important components of the skin barrier, notably *FLG*, *SPINK5*, and corneodesmosin.⁴ Others and we have also found genetic associations specifically with eczema-asthma comorbidity. Marenholz et al⁵ identified 7 susceptibility loci for the combined eczema and asthma phenotype. These loci were enriched for known eczema loci, further strengthening the case for the involvement of epithelial barrier integrity in allergic disease progression. Two of the loci, *IL4/KIF3A* and *LRRC32*, were only associated with combined eczema and asthma. Our group also found that *KIF3A* genetic variation is specifically associated with eczema-asthma comorbidity.⁶ Although the

mechanism for this is currently unclear, it is likely to be systemic because KIF3A is widely expressed and present in both primary and motile cilia.

Notably, there is evidence that the skin barrier plays a role in allergic sensitization even in the absence of eczematous lesions. A recent cohort study found that transepidermal water loss in new-borns was associated with food allergy at 2 years of age regardless of eczema status and controlling for parental atopy.⁷ Transepidermal water loss is an established measure of skin barrier function, and these results support that a faulty skin barrier even in the absence of eczema can promote systemic sensitization. The study also suggests that the concept of the atopic march may need to be redefined to account for the possibility of cutaneous sensitization through an impaired skin barrier, leading to later development of allergic airway disease in the absence of overt eczema.

Food allergy has a significant degree of comorbidity with other childhood allergic diseases, and a hypothetical model of the atopic march should account for the role of food sensitization. The association between food sensitization and eczema has been demonstrated numerous times, but the mechanism has remained unclear. A recent review revealed a potential immunologic pathway that links the skin barrier to the gut⁸ whereby a faulty skin barrier and eczema result in an intestinal mastocytosis characterized by interleukin 9–producing mucosal mast cells, resulting in increased clinical reactivity to ingested food allergens. The role of these cells in the atopic march remains to be determined.

Numerous studies with animal models support the role of the skin barrier in atopic disease.⁴ Epicutaneous sensitization to ovalbumin through an impaired skin barrier predisposes mice to increased airway responsiveness on challenge with aerosolized ovalbumin. Other studies have suggested that the epithelial cytokine thymic stromal lymphopoietin, which is overexpressed in the skin of mouse eczema models, may be a link between eczema and airway hyperresponsiveness.

A proper understanding of causality in the progression of childhood allergic disease is important for the development of effective treatment strategies. A clearly demonstrated relationship between early sensitization through a compromised skin barrier and the later development of asthma and AR might allow intervention strategies to prevent allergic disease from developing. An often discussed approach is the strengthening of the skin barrier in at-risk children before eczematous lesions appear to prevent cutaneous sensitization.⁹ Studies have found that use of topical emollients soon after birth can lower the risk of eczema.^{4,10} In principle, strengthening of the skin barrier before the onset of eczema may halt the development of not only eczema but also subsequent allergic diseases. Randomized clinical trials to test this type of strategy are currently under way. Results from these studies may provide important information to help resolve the question about the role of the skin barrier in the atopic march.

In conclusion, evidence from genetic association studies, cohort studies, and experimental animal models support the hypothesis that there is a relationship between epithelial barrier dysfunction and the later development of asthma and AR that involves cutaneous sensitization through an impaired skin barrier in a subset of individuals. However, this may

occur with or without the presence of eczema. The presence of eczema is simply a marker of the faulty barrier, which may be systemic. There is strong emerging evidence that a faulty epithelial barrier in early life is associated with systemic sensitization even in the absence of eczema, which may in part account for the observed phenotypical heterogeneity of allergic disease comorbidity. An increased understanding of the complex mechanisms involved in allergic disease progression will allow early, personalized intervention based on each child's set of genetic, familial, and environmental risk factors.

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