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REVIEW ARTICLE

Review Series: Immune Responses in the Host-Environment Interface - Understanding the Mechanisms of Allergic Sensitization

Epicutaneous Immunity and Onset of Allergic Diseases - Per-"Eczema"tous Sensitization Drives the Allergy March

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ABSTRACT

Results from recent epidemiological studies strongly suggest that ingestion of food promotes immune tolerance to food antigens, whereas exposure to food antigens through skin leads to allergic sensitization. A "dual-allergen-exposure hypothesis" has been proposed to explain those findings. However, several other recent studies have demonstrated that some allergic diseases can be successfully treated by recurrent epicutaneous exposure to allergens. At a glance, these two sets of findings seem to be contradictory, but we think they provide important clues for understanding the mechanisms behind the allergy march.

Here, we propose that per-"eczema"tous sensitization drives the allergy march, and we introduce results from several published studies in support of this hypothesis. We hope that this review may help in establishment of new strategies for preventing the allergy march in the near future.

KEY WORDS

alarmin, allergy march, eczema, epicutaneous sensitization, food allergy

INTRODUCTION

The allergy march is defined as the progression of allergic diseases in infancy from food allergy and atopic dermatitis to asthma and rhinoconjunctivitis.[1] During this march, both the offending allergens and the affected organs change (Table 1). The exact underlying mechanisms of why and how the antigens change have not been fully elucidated, but an immune predisposition towards Th2 is likely to play an important role.

In this review, we propose a hypothesis that per-"eczema"tous sensitization drives the allergy march, and we introduce results from several published studies to support the validity of this hypothesis.

DUAL-ALLERGEN-EXPOSURE HYPOTHESIS

Oral Tolerance

All vertebrate animals with jaws eat plant and/or animal proteins. The animals' intestinal tract digests and absorbs foreign proteins without inducing harmful immune responses in the host. This is very important and is called "oral tolerance." In animal models, immune responses—including specific IgE antibody production—to intravenously or intraperitoneally administered or transplanted antigens were almost completely prevented when the antigens were orally administered beforehand.[2] Subsequent studies indicated that intestinal microbiota,[3] especially indigenous *Clostridium* species,[4] are critical for induction of oral tolerance in animal models.

In 2008, Du Toit *et al*. demonstrated that Jewish children in the UK have an almost 10-fold higher prevalence of peanut allergy compared with Jewish children in Israel, and they found that Israeli infants are fed peanut products in large quantities in the first year of life, whereas UK infants do not.[5] This observation clearly demonstrates that induction of oral tolerance via early intake seems to inhibit subsequent development of food allergy. In a similar context, mater-

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Table 1 Allergens and affected organs in the allergy march

Disease	Major allergens	Affected organs
Food allergy	Food	Skin, Intestine, Mucosa
Atopic dermatitis	*Staphylococcus aureus*	Skin
	Food, Airborne-antigens	
	Fungal protein MGL_1304 †	
Asthma	House dust mite, fungi	Lung
Rhinoconjunctivitis	Pollen, fungi	Nose, eyes

† An antigen from *Malassezia globosa* was recently identified in perspiration (*J Allergy Clin Immunol*. DOI: 10.1016/j.jaci.2013.03.047).

nal dietary antigen avoidance during pregnancy or lactation with the goal of preventing atopic diseases in the child is no longer recommended.[6,7]

Epicutaneous Sensitization?

In 2003, Lack *et al*. analyzed prospective cohort data from more than 1,300 preschool children in the UK and demonstrated that a convincing history of peanut allergy was significantly associated with the use of skin preparations containing peanut oil (odds ratio, 6.8; 95% confidence interval, 1.4 to 32.9).[8] A subsequent study reported that peanut protein was undetectable in skin preparations containing peanut oil,[9] but the environmental presence of peanut allergen, such as on tabletops or on hands after applying peanut butter, even after washing with water alone (no soap), could represent another source of topical exposure.[10] Add in the facts that biologically active peanut protein in household dust is related to household peanut consumption[11] and that household peanut consumption is a risk factor for development of peanut allergy[12] and it seems clear that epicutaneous exposure to food antigens is a risk factor for food allergy, presumably through epicutaneous sensitization.

In 2008, Lack postulated a new "dual-allergen-exposure hypothesis" that ingestion of food promotes immune tolerance to food antigens, whereas exposure to food antigens through skin facilitates allergic sensitization.[13] Several lines of evidence support that hypothesis, including that loss-of-function variants in the filaggrin gene (*FLG*) are a significant risk factor for peanut allergy.[14] Filaggrin is expressed only in the skin, not in the intestinal wall or bronchi, suggesting that impaired barrier function of the skin but not of the intestine may facilitate epicutaneous antigen uptake and lead to allergic sensitization.

Recently in Japan, nearly 2,000 newly-diagnosed wheat-allergy adults were reported to have become sensitized by using a special facial soap containing hydrolyzed wheat protein.[15] This also points to the importance of epicutaneous exposure in development of food allergy. Of note, these patients had shown no symptoms upon ingestion of wheat products before use of the soap, suggesting that epicutaneous sensitization can occur even in individuals with established oral tolerance. In a mouse model, recurrent epicutaneous peanut exposure induced IgE-synthesis, and it prevented induction of oral tolerance to peanuts and even partially abrogated existing tolerance to peanuts.[16]

EPICUTANEOUS TOLERANCE?

In 2009, Senti *et al*. reported treating seasonal pollen allergy patients in a monocentric, placebo-controlled, double-blind trial by epicutaneous administration of vaseline patches containing grass pollen allergen.[17] Treatment took place before and during the pollen season, and allergen-treated patients showed significantly decreased scores in nasal provocation tests and clinical symptoms during the pollen season. By 2012, eight studies had successfully used similar epicutaneous antigen exposure methods in patients with pollen allergies and patients with food allergies.[18] A number of animal studies have followed up the efficacy.[19,20]

High molecular weight proteins had been thought to be unabsorbable via the skin. However, a recent study demonstrated that although they cannot be absorbed through intact skin, but they can be taken up by dendritic cells,[19] especially through hair follicles.[21] In addition, the major T cell phenotype emigrating from the skin during a cutaneous immune response in mice was reported to be activated regulatory T cells with high expression of Foxp3, a T-cell master gene having a regulatory property.[22,23] This observation strongly suggests that the skin is a tolerogenic organ.

DO EPICUTANEOUSLY ADMINISTERED ANTIGENS INDUCE ALLERGIC SENSITIZATION, OR TOLERANCE?

A carefully conducted animal study provided intriguing information that intact skin, not stripped skin, is crucial for the safety and efficacy of peanut epicutaneous immunotherapy.[24] In fact, prospective cohort studies demonstrated eczema to be a risk factor for hen's egg allergy[25] and peanut allergy.[8,26] Sensitization to latex was also strongly associated with the presence of hand eczema.[27]

These clinical and experimental observations strongly indicate that exposure of eczematous skin, but not intact skin, to food proteins is a true risk fac-

Table 2 Proposed factors associated with per-eczematous sensitization

Skin Barrier Damage	
	Scratching
	Protease antigens
	Increase in pH of the skin
Alarmin/DAMPs (damage-associated molecular patterns)	
	Eosinophil-derived neurotoxin (EDN)
	IL-33
	Histamine
Microbe-associated Adjuvant	
	Staphylococcal superantigens
Cytokines Produced by Keratinocytes	
	Thymic stromal lymphopoietin (TSLP)
Phenotype of Antigen-presenting Cells	
	IgE-bearing Langerhans cell (LC)

tor for sensitization to food antigens.

ECZEMA IS A STRONG RISK FACTOR FOR SUBSEQUENT DEVELOPMENT OF ALLERGIC DISEASES

Infants often suffer from various types of dermatitis. In an earlier prospective cohort study, we looked for associations between various types of dermatitis in infancy and subsequent development of allergic symptoms.[28] Analyses of infants with four types of dermatitis (infantile eczema, seborrheic dermatitis, intertrigo and diaper dermatitis) that manifested independently in the first month of life showed that neonates with infantile eczema were diagnosed with atopic dermatitis significantly earlier and had a significantly higher prevalence of wheezing than infants without infantile eczema until 2 years of age. In addition, a recent large-scale cohort study concluded that eczema in infancy might have a causal effect on hay fever in children with, and perhaps without, asthma.[29]

It has also been clearly demonstrated that atopic dermatitis at age 2 or 3 can predict subsequent development of asthma both in the general population[30] and in wheezing children.[31] This is the typical natural course of allergic diseases in young children (allergy march).[1]

WHY DOES PER-"ECZEMA"TOUS SENSITIZATION SKEW IMMUNE RESPONSES TOWARDS TH2?

In eczematous lesions, the skin barrier function is usually impaired. However, an animal model with simple barrier dysfunction, such as *filaggrin* (*flg*)-mutation (ft/ft mice), exhibited a Th17-skewing but not Th2-skewing sensitization pattern.[32] This suggests involvement of some other factor(s) in allergic sensitization that occurs when eczematous skin is exposed to antigens. Table 2 summarizes the factors proposed as promoting Th2-immune responses in eczematous lesions.

Skin Barrier Damage

Mechanical skin injury (tape stripping) induced a Th2 immune response in the draining lymph nodes in a damage-dependent manner,[33] at least in part by inducing cutaneous thymic stromal lymphopoietin (TSLP) expression.[34] Scratching skin may cause epithelial cell and endothelial cell damage and allow release of damage-associated molecular patterns (DAMPs); this will be discussed later.

Protease Antigens

A major airborne antigen, house dust mite, is known to have protease activity.[35,36] Topical application of such proteases not only reduces barrier function of the skin, which increases permeability,[37] but also activates protease-activated receptor 2, which delays epidermal barrier recovery.[38] In addition, protease activity in the skin causes IL-33/ST2-dependent immune responses[39] and enhances TSLP production.[40]

Increase in pH

An increase in skin pH has been demonstrated in patients with eczema[41] or *FLG*-loss-of-function mutations.[42] An increased pH in the stratum corneum leads to degradation of lipid-processing enzymes (necessary for production of natural moisturizing factor from filaggrin molecules)[43] and facilitates *Staphylococcus aureus* (*S. aureus*) growth.[44]

Alarmin/DAMPs

One of the biggest advances in immunology in recent decades is the discovery that immune systems are activated by recognition of damaged cells.[45] The specific molecular patterns triggering this are called "alarmins" or DAMPs.[46]

Eosinophil-derived neurotoxin, one of the major granular proteins in eosinophils, can act as an alarmin to activate dendritic cells and trigger Th2 immune responses.[47] In our aforementioned cohort study, we found significant eosinophilia in the cord blood of neonates who developed infantile eczema compared with those without infantile eczema, suggesting involvement of eosinophils in subsequent development of atopic dermatitis or wheeze.[28]

IL-33, a member of the IL-1 family, is constitutively expressed in the nucleus of endothelial cells and epithelial cells *in vivo*[48] and is released upon cellular damage, but not during apoptosis.[49] Keratinocyte lysate contains biologically active IL-33 protein.[50] This novel cytokine reportedly activates a number of different cell types, including mast cells, tissue residual cells and type 2 innate lymphoid cells (ILC2), and it probably plays critical roles in the development of allergic diseases.[51]

Staphylococcus-Derived Superantigens

S. aureus infection is one of the most frequent causes

of acute exacerbation of atopic dermatitis, and impaired local bactericidal activity has been reported in atopic skin.[52] *Staphylococcus*-derived superantigens are known to directly cause dermatitis of the skin[53] and induce IgE synthesis.[54] Notably, superantigen-induced immune reactions are only partially inhibited by corticosteroids.[55]

Phenotype of Antigen-Presenting Cells

Langerhans cells, which are skin-dwelling, professional antigen-presenting cells, are known to play critical roles in the induction of atopic dermatitis-like inflammation[56] as well as antigen-specific IgE synthesis.[57] A recent study demonstrated that signaling through TSLP is indispensable for this dermatitis-like inflammation[56] and Th2 polarization.[58]

Langerhans cells express high-affinity IgE receptors (FcεRI), especially in atopic individuals.[59] In a mouse model, FcεRI engagement of Langerhans cell-like dendritic cells induced accumulation of Th2 cells in the skin, whereas another IgG-bearing type of dendritic cell, the so-called "inflammatory dendritic epidermal cell (IDEC)", caused Th1 cell accumulation.[60]

CONCLUSIONS

In this review we proposed that per-"eczema"tous sensitization drives the allergy march, and we presented evidence in support of this hypothesis. We strongly hope that authors of earlier clinical studies will revisit their data and patients and look for possible involvement of eczema in the development of food allergy and other allergic diseases, as well as for possible effects of *FLG*-mutations or environmental food antigen exposure.

We also hope that clinical trials will investigate intervention in infantile eczema with the goal of preventing allergic sensitization, especially to food antigens. It is our fervent hope that this review will facilitate early development of novel strategies for preventing the allergic march.

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