Prevention of food allergy

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The past few decades have witnessed an increase in the prevalence of IgE-mediated food allergy (FA). For prevention strategies to be effective, we need to understand the causative factors underpinning this rise. Genetic factors are clearly important in the development of FA, but given the dramatic increase in prevalence over a short period of human evolution, it is unlikely that FA arises through germline genetic changes alone.
A plausible hypothesis is that 1 or more environmental exposures, or lack thereof, induce epigenetic changes that result in interruption of the default immunologic state of tolerance. Strategies for the prevention of FA might include *primary prevention*, which seeks to prevent the onset of IgE sensitization; *secondary prevention*, which seeks to interrupt the development of FA in IgE-sensitized children; and *tertiary prevention*, which seeks to reduce the expression of end-organ allergic disease in children with established FA. This review emphasizes the prevention of IgE-mediated FA through dietary manipulation, among other strategies; in particular, we focus on recent interventional studies in this field. (J Allergy Clin Immunol 2016;137:998-1010.)

Key Words: *Food allergy, atopic dermatitis, peanut allergy, cow's milk allergy, egg allergy, oral food challenge, specific IgE*

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Abbreviations used
AD: Atopic dermatitis
aOR: Adjusted odds ratio
CMA: Cow's milk allergy
CoFAR: Consortium of Food Allergy
EAT: Enquiring About Tolerance
FA: Food allergy
FLG: Filaggrin
HEAP: Hens Egg Allergy Prevention
ITT: Intention to treat
LEAP: Learning Early About Peanut Allergy
NNT: Number needed to treat
OFC: Oral food challenge
OR: Odds ratio
PA: Peanut allergy
RR: Relative risk
sIgE: Specific IgE
SPT: Skin prick test
STAR: Solids Timing for Allergy Research
TEWL: Transepidermal water loss
UK: United Kingdom

In many countries, food allergy (FA) is now considered a significant public health concern, affecting 3% to 6% of children in the developed world.[1,2] FA results in significant morbidity, but fatalities are rare.[3] A diagnosis of FA has been shown to negatively influence quality of life for patients and their families, and poses a significant financial burden.[4,5]

There are many risk factors associated with the development of FA, including atopic family history, male sex (at least in childhood), ethnicity, atopic dermatitis (AD), and related genetic polymorphisms. Although genetic factors are clearly important in the development of FA, its increase in prevalence has occurred over a short period of human evolution, implying that FA does not arise as a result of germline genetic changes alone. Therefore it seems plausible that 1 or more environmental exposures, or lack thereof, can induce epigenetic changes that interrupt the default immunologic state of tolerance to foods. This has stimulated ongoing research into the identification of modifiable environmental factors (including nutrition, the intrauterine environment, and lifestyle factors) that might play a role in gene expression through epigenetic modification.[6]

When explaining the increase in FA, one dominant theory is the hygiene hypothesis,[7] which posits that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (such as gut flora or probiotics), and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system. However, the recent publication of randomized trials, such as the Learning Early About Peanut Allergy (LEAP)[8] and Enquiring About Tolerance

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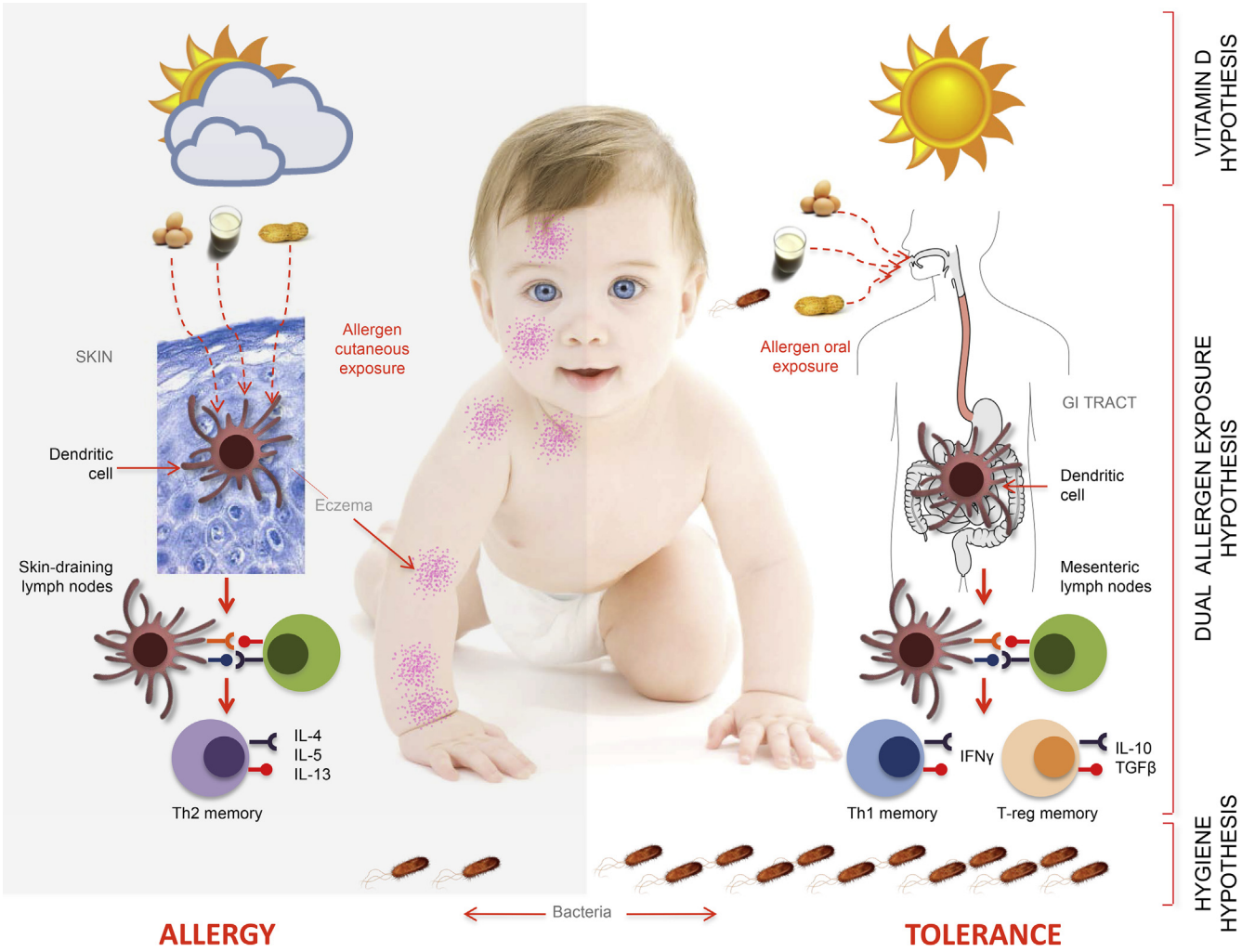

FIG 1. Integration of the vitamin D deficiency, hygiene, and dual-allergen exposure hypotheses. Sufficient levels of vitamin D, a diverse microbiota, and oral allergen exposure collectively support the development of tolerance. Conversely, allergic sensitization is promoted through cutaneous exposure, reduced diversity of microbiota, and vitamin D deficiency. Diminished microbial diversity and vitamin D deficiency are thought to interrupt the regulatory mechanisms of oral tolerance, with the latter also contributing to decreased epidermal barrier function. *GI*, Gastrointestinal; *T-reg*, regulatory T cells. Graphic modified from Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol 2008;121:1331-6. Copyright © 2008 Elsevier. Reprinted with permission.

(EAT)[9] studies, has given support to the notion of oral tolerance induction, consistent with the dual-allergen exposure hypothesis (Fig 1).[10] The latter suggests that early cutaneous exposure to food protein through a disrupted skin barrier leads to allergic sensitization, whereas early oral exposure to food allergen induces tolerance. Additional theories relate to other environmental factors; for example, vitamin D might be required for regulatory immunologic mechanisms that are important in preventing FA and establishing oral tolerance. These integrated hypotheses provide a framework for research focused on the prevention of FA. However, investigations in this field are often hindered by methodological limitations (Table I).

In this review, we briefly cover the role of nonmodifiable genetic factors before highlighting cross-sectional studies and recent interventional studies in the field of allergy prevention through dietary manipulation.

NONMODIFIABLE FACTORS

Genetics

A family history of FA is itself a risk factor for FA. For instance, a child has a 7-fold increase in risk of peanut allergy (PA) if there is a parent or sibling with PA.[11]

The complex interplay between genetic and environmental factors giving rise to FA is perhaps best demonstrated by comparing concordance rates for allergy between genetically identical (monozygotic) and nonidentical (dizygotic) subjects. Although previous twin studies have estimated a high degree of heritability for atopic diseases, such as asthma (87%),[12] and AD (74%),[13] a study by Sicherer et al[14] of 58 twin pairs estimated the heritability for PA to be as high as 82% to 87%. In a recent review, Hong et al[15] highlighted more than 10 genes (several involved in allergen presentation, a T_H2-skewed immune system, or both) that have been associated with FA or food sensitization. However, genetically determined skin barrier