

Genes and the environment: Two readings of their interaction

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House dust mites have been recognized as important allergens for atopic dermatitis, allergic rhinitis, and particularly asthma in children and in adults. The presence of sensitization to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* has been related to both the new onset of disease and the severity of the clinical manifestation.¹ The seemingly apparent implication of such findings was that the level of environmental exposure to the allergen eliciting such an IgE antibody response was the culprit for both the incidence and the severity of the ensuing disease. Indeed, a seminal paper by Sporik et al² reporting an admittedly small study in 1990 not only suggested such a relation but also proposed that it has a characteristic configuration, namely a threshold beyond which the exposure affects the incidence of asthma. Thresholds for the effects of house dust mite exposure on atopic sensitization to house dust mites and asthma exacerbations have subsequently been reported.³

Since then, numerous studies have addressed this topic and put into question the relevance of house dust mite exposure for the development of specific IgE antibodies toward these allergens.⁴⁻⁸ A lot of controversy has arisen reflecting a variety of underlying concepts: (1) the mere presence of the allergen is sufficient to elicit an IgE mediated immune response, (2) above a certain threshold of exposure, allergen exposure induces sensitization, (3) the level of exposure matters inasmuch as increasing levels result in an increased risk of sensitization, and (4) the level of exposure matters but the relation is not linear: at high levels of exposure tolerance is induced. In the article by Hunninghake et al⁹ published in this issue of the Journal, a fifth concept is proposed: the level of exposure to house dust mites matters but depends on an exposed subject's genetic background with respect to polymorphisms in the *IL10* gene. One has to bear in mind, however, that the study by Hunninghake et al⁹ is not based on a general population sample but enrolled only subjects with asthma. Because asthma may result in an increased local production of IgE in the airway mucosa as a consequence of the disease,¹⁰ the findings presented in this issue of the Journal may not be representative of the general population or relevant for IgE production to house dust mites in nonaffected subjects or subjects with atopic dermatitis.

The debate is even fiercer when it comes to the role of house dust mite exposure for the new onset of asthma. Although exposure to *D pteronyssinus* and *D farinae* was put forward as a causal agent in some reports, others did not find any relation between exposure and the incidence of the illness. Part of this controversy may be attributable to the complex nature of asthma, which resembles a syndrome rather than a distinct clinical entity.¹¹ Different phenotypes are likely to open out into 1 clinical manifestation that cannot be traced back to the various underlying mechanisms. Yet in population-based studies, different phenotypes can be distinguished by their natural course and their associated features. A number of prospective studies have clearly shown that the asthma phenotype that goes along with the development of atopic sensitization very early in life is predisposed to a chronic, relapsing, and more severe course than the nonatopic phenotype.^{5,12} Interestingly, the level of house dust mite exposure concomitantly with the initiation of IgE antibodies toward that allergen early in life impaired lung function at school age in this group of children.⁵ Thus, a distinct asthma phenotype may be responsive to such environmental stimuli, whereas other phenotypes may not be affected by house dust mite exposure at all. This reasoning may apply not only to the new onset of asthma but also to trigger factors of the disease. Whether the mite-susceptible asthma phenotype relies on immune responses modified by levels of IL-10 as suggested by the findings of Hunninghake et al⁹ remains to be seen.

Interestingly, the authors have taken an upside-down approach and entitled their paper, "Dust mite exposure modifies the effect of functional *IL10* polymorphisms on allergy and asthma exacerbations" rather than "*IL10* polymorphisms modify the effect of house dust mite exposure on sensitization and asthma exacerbations." In epidemiologic studies, associations between 2 or more variables are investigated, and various measures of the strength of association between these variables are reported. However, from such analyses, the direction of the association cannot be deduced: A can result in B as well as B can result in A. The view taken by Hunninghake et al⁹ implies that any environmental exposure can influence the effect of a functional promoter polymorphism in a given gene. Thereby, the function of a genetic variant may not be written in stone but may be amenable to modification through environmental exposures. In this specific example, low levels of house dust mite exposure may result in increased gene expression, whereas high levels might decrease IL-10 expression in carriers of this particular variant.

There are experimental studies supporting such a view. A polymorphism in the promoter of *IL-13*, a key cytokine in asthmatic airway inflammation, enhanced *IL-13* promoter activity in primary human and murine CD4⁺ T_H2 lymphocytes, whereas the same *IL13-1112T* polymorphism had opposite transcriptional effects in nonpolarized CD4⁺ T cells.¹³ The nuclear

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milieu may thus determine the functional outcome of a genetic variation. The nuclear milieu in turn may be affected by the extracellular environment that will eventually be modified by a subject's environmental exposures. Therefore, it is conceivable that house dust mite exposure modifies gene expression levels of IL-10, particularly because IL-10 is released at the end of multiple immune response pathways. Measurements of IL-10 levels in these populations could help clarify the issue. Whatever the direction of the interaction might be, an essential part of gene*environment interactions is the fact that both components are necessary but not sufficient on their own, as elegantly highlighted by Hunninghake et al⁹ in this issue of the Journal. Gene*environment interactions are contextual, and neither the environmental nor the genetic contribution to asthma exacerbations can be adequately assessed without taking the counterpart into consideration.

For a clinician, gene*environment interactions may in the near future become an important target when attempting to individualize patient treatment. In the context of house dust mite exposure and asthma exacerbations, one might wonder whether studies investigating the potential benefit of various allergen avoidance measures should include markers of susceptibility to allergen exposure. Such markers may be based on clinical grounds (symptoms triggered by dusty environments, nasal challenge, and so forth) but may increasingly also take genetic variation into account. Whether IL-10 polymorphisms contribute to the variability of response to allergen avoidance measures remains to be elucidated.

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