

Correspondence

Adaptive immunity as a determinant of allergenicity

To the Editor:

Traidl-Hoffman et al¹ discuss in a creditable way the numerous elements that contribute to the allergenicity—that is, the T_H2-deviating (or sensitizing) capacity of proteins. Therefore, we were left surprised, because the role of adaptive immunity was largely dismissed. Overstating a little, the review drew a picture in which an allergenic protein is a kind of coincidental bystander in the process that results in the production of specific IgE, as if the only properties for a protein to be an allergen are that it is in the right place, at the right time, and it is immunogenic. If this were the case, the number of allergenic proteins per source should be enormous.

Because only few proteins from an allergen source are allergens and most are not, the immune system must make a distinction between them. As discussed in the review, innate immunity and factors related to it play important roles in sensitization, but it is the adaptive immune system that confers specificity to the immune response—that is, “selects” the allergens.

For the development of a specific immune response, the recognition of antigenic peptides by the antigen receptor of T lymphocytes (TCR) on antigen-presenting cells is one of the pivotal steps. It has been clear since the 1990s that the extent of TCR ligation affects the differentiation of T cells into T-cell subsets.² Simplifying, weak stimulation through TCR favors T_H2-type responses, whereas strong stimulation favors T_H1-type responses.² Because of the nature of the thymic selection process, clearly foreign substances, such as microbial antigens, are recognized with a high TCR avidity (“optimally”), whereas self-antigens (and presumably evolutionary close antigens in general) with a low TCR avidity (“suboptimally”). A collateral phenomenon is that a low peptide density on antigen-presenting cells also provokes a weak stimulus for T cells.² This latter observation is well in line with the fact that low ambient allergen concentrations favor T_H2 deviation, whereas high ambient allergen concentrations can be tolerogenic.³

As underscored in the review, mechanisms directly (eg, enzyme activity) or indirectly (eg, adjuvantlike substances) linked to allergens explain the allergenicity of proteins in only a minority of cases. A good example of an important allergen group the allergenicity of which is not explained by the mechanisms reviewed is the lipocalins.⁴ They contain almost all significant respiratory mammalian allergens. Surprisingly, they are poorly immunogenic, weakly antigenic *in vitro*, and the T-cell epitopes examined are recognized suboptimally by human T cells (a Can

f 1 epitope; Juntunen R, unpublished data, March, 2006).^{4,5} Why are they then allergenic? A justified hypothesis is that lipocalin allergens often exhibit an amino acid identity of 40% to 60% with endogenous human proteins, and therefore, they are not recognized optimally.^{4,6} In this context, it is logical that animal food allergens above a homology level of about 60% with human proteins are rarely allergenic⁷ because they are probably too similar with the immunologic self. In agreement with this view, the amino acid identity of a recently identified respiratory dog allergen, Can f 5 (prostatic kallikrein), is about 60% with human prostate-specific antigen.⁸

Taken together, we see that adaptive immunity cannot be dismissed as a factor involved in the development of a specific T_H2-deviated immune response. For some proteins, such as lipocalins, evolutionary relatedness with human proteins (sequential homology) can be the causative link. Proteins at the borderline of self and nonself may be inherently prone to induce a T_H2-deviated immune response.

Tuomas Virtanen, MD, PhD

Tuure Kinnunen, MD, PhD

From the Department of Clinical Microbiology, University of Kuopio, Finland. E-mail: tuomas.virtanen@uku.fi.

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REFERENCES

1. Traidl-Hoffmann C, Jakob T, Behrendt H. Determinants of allergenicity. *J Allergy Clin Immunol* 2009;123:558-66.
2. Leitenberg D, Bottomly K. Regulation of naive T cell differentiation by varying the potency of TCR signal transduction. *Semin Immunol* 1999;11:283-92.
3. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;357:752-6.
4. Virtanen T, Kinnunen T. Mammalian allergens. In: Lockey RF, Ledford DK, editors. *Allergens and allergen immunotherapy*. 4th ed. New York: Informa Healthcare USA, Inc; 2008. p. 201-18.
5. Kinnunen T, Buhot C, Näränen A, Rytönen-Nissinen M, Saarelainen S, Pouvelle-Moratille S, et al. The immunodominant epitope of lipocalin allergen Bos d 2 is sub-optimal for human T cells. *Eur J Immunol* 2003;33:1717-26.
6. Virtanen T, Zeiler T, Rautiainen J, Mäntylä R. Allergy to lipocalins: a consequence of misguided T-cell recognition of self and nonself? *Immunol Today* 1999;20:398-400.
7. Jenkins JA, Breiteneder H, Mills EN. Evolutionary distance from human homologs reflects allergenicity of animal food proteins. *J Allergy Clin Immunol* 2007;120:1399-405.
8. Mattsson L, Lundgren T, Everberg H, Larsson H, Lidholm J. Prostatic kallikrein: a new major dog allergen. *J Allergy Clin Immunol* 2009;123:362-8.

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