Correspondence

Reply

To the Editor:

We thank Virtanen and Kinnunen[1] for the comments on our article "Determinants of allergenicity."[2] We certainly agree that adaptive immunity constitutes an important determinant of allergenicity, and we had no intention to dismiss its essential role in the development of allergic immune responses. As outlined in the review, the specific recognition of allergens by T cells and subsequent T_H2 differentiation is a prerequisite for the development of type I hypersensitivity reactions. Different mechanisms influence the initial T_H2 polarization that includes the degree of T cell receptor (TCR) ligation (signal 1), the type of costimulatory signals (signal 2), and cytokines/mediators present during antigen presentation (signal 3). We agree that the extend of TCR ligation affects T-cell differentiation and that allergenicity is also determined in part by peptide density and TCR avidity during antigen presentation, which we have reviewed elsewhere.[3] It is out of question that the adaptive immune response is central, but it is also out of question that this process is strongly influenced by factors that go beyond the classic signals 1, 2, and 3. The major goal of our review was to outline that if we want to understand the old question of what makes the allergen an allergen, we have to look beyond the classic concepts and integrate additional aspects that have largely been ignored in the past. In recent years, the research community has begun to realize that, aside from allergen structure and function, adjuvant factors derived from allergen carriers such as proinflammatory enzymes,[4] bioactive lipids,[5,6] or biogenic and anthropogenic environmental factors[7] that are present during natural exposure conditions clearly can influence the outcome of the immune response. Because we believe that this is an important and expanding research direction, we focused our review on these issues.

Using the example of lipocalins, Virtanen and Kinnunen[1] raised the issue of evolutionary relatedness as a determinant of allergenicity and hypothesize that because of a high degree of homology with endogenous human proteins, lipocalins are recognized suboptimally by human T cells, which in turn may favor the development of T_H2 responses. They suggest that proteins at the borderline of self and nonself are prone to induce T_H2 responses and that this is determined at the level of T-cell recognition. This is an intriguing concept that certainly warrants further investigation. Interestingly, homology to endogenous proteins may also influence allergenicity independent of TCR recognition at the level of innate immunity. A molecular mimicry of Der p 2 that can substitute for MD-2 in the LPS receptor complex and thus act as an autoadjuvant in the sensitization process has recently been reported.[8] This may be a rare exception, but it may also be the first report that opens a new and exciting field in which functional mimicry of allergens and pathogen recognition receptors will be recognized as an additional determinant of allergenicity.

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REFERENCES

1. Virtanen T, KinnunenT. Adaptive immunity as a determinant of allergenicity. J Allergy Clin Immunol 2009;■■■:■■■-■■.
2. Traidl-Hoffmann C, Jakob T, Behrendt H. Determinants of allergenicity. J Allergy Clin Immunol 2009;123:558-66.
3. Jakob T, Traidl-Hoffmann C, Behrendt H. Dendritic cells—the link between innate and adaptive immunity in allergy. Curr Allergy Asthma Rep 2002;2:93-5.
4. Boldogh I, Bacsi A, Choudhury BK, Dharajiya N, Alam R, Hazra TK, et al. ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. J Clin Invest 2005;115:2169-79.
5. Traidl-Hoffmann C, Kasche A, Jakob T, Huger M, Plotz S, Feussner I, et al. Lipid mediators from pollen act as chemoattractants and activators of polymorphonuclear granulocytes. J Allergy Clin Immunol 2002;109:831-8.
6. Traidl-Hoffmann C, Mariani V, Hochrein H, Karg K, Wagner H, Ring J, et al. Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. J Exp Med 2005;201:627-36.
7. Alessandrini F, Schulz H, Takenaka S, Lentner B, Karg E, Behrendt H, et al. Effects of ultrafine carbon particle inhalation on allergic inflammation of the lung. J Allergy Clin Immunol 2006;117:824-30.
8. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R, et al. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. Nature 2009;457:585-8.

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