

Immunologic effect of immunotherapy

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The principle of treating allergic diseases by injection of increasing amounts of the allergen causing the symptoms has been used for almost a century (1). Specific immunotherapy (SIT) for IgE-mediated allergy has been shown to be effective in reducing symptoms of hay fever and asthma in selected patients and even more so in venom anaphylaxis (2). The study of the mechanisms of SIT has served as a model to gain insight into the immunologic changes associated with allergic diseases, and is also a prerequisite for improving the efficacy and safety of SIT. For many years, the focus has been on the changes in the specific immunoglobulins IgE and IgG during SIT, but the last decade has directed attention to the changes in T-cell responses and cytokines (3–8).

Allergen-specific immunoglobulins

During SIT, an initial increase in specific IgE is seen, followed by a slow decrease over many months to a level near the baseline level (9). The seasonal increase in specific IgE seen in pollen-sensitive allergics is blunted by SIT (10). Specific IgG4 increases in a dose-dependent manner during the first months of SIT to a level 5–10 times higher than baseline. In contrast to specific IgE, IgG4 remains at this high level as long as SIT is administered. Although the increase in IgG4 depends on the dose of allergen given, no correlation between the level of specific IgE or IgG4 and the clinical response to SIT can be demonstrated during or after discontinuation of SIT (11, 12).

Effector cells, T_{H1} and T_{H2} CD4⁺ cells, and cytokines

About 10 years ago, two subsets of CD4⁺ cells were recognized in mice, characterized by their different cytokine profiles: T_{H2} cells mainly producing IL-4 and

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IL-5, later found also to produce IL-13 in man; and T_H1 cells producing IFN- γ and IL-2. T_H2 cells are predominant in allergic individuals (13), and IL-4 and IL-13 promote IgE heavy chain switching in B cells, increasing IgE, while IL-5 promotes eosinophil differentiation, activation, and survival. In nonallergics, the allergen-specific T cells are T_H1 cells, and the cytokines IFN- γ and IL-2 activate macrophages. IFN- γ also has an inhibitory effect on IgE synthesis.

The number, activity, and distribution of effector cells, mast cells, and eosinophils are influenced by SIT. A decrease in cutaneous mast cells, as well as nasal mast cells and their activity, has been demonstrated after SIT in grass- and ragweed-pollen-sensitive allergics. Likewise, a decreased number of eosinophils has been demonstrated in the skin, nose, and bronchi after SIT (2, 3).

There is a general consensus that SIT is associated with a shift in the cytokine profile from a predominant T_H2 cytokine profile to a T_H1 profile in allergics. Accordingly, studies in mice (14) and man (15) have demonstrated that exposure to a low allergen dose, a model of natural allergen exposure, is associated with increased IL-4 production, while higher doses of allergen, as administered during SIT, are associated with a decrease in IL-4 and an increase in IFN- γ production.

Several different mechanisms seem to lead to the shift in cytokine production. The hypothesis that anergy, i.e., an induced antigen-specific unresponsiveness by T cells, is a possible mechanism is supported by a study by Akdis et al.

(16), in which bee-allergics were treated with SIT, resulting in a decrease in both T_H2 and T_H1 cytokines. The specifically tolerized T cells from the patients were then stimulated with allergen in the presence of either IL-2 or IL-15. The T cells responded with T_H1 cytokine production, while the presence of IL-4 partly restored T_H2 -cell cytokine production. Another possible mechanism is immune deviation, i.e., a shift in the T_H1 / T_H2 balance from the predominantly T_H2 -like T-cell population usually found in allergics to the more T_H1 -like T-cell population seen in nonatopics. This mechanism is supported by a number of studies showing the shift in cytokine profile during SIT. In bee-venom-sensitive patients treated after an ultrarush SIT protocol, Jutel et al. demonstrated a decreased secretion of IL-4 and IL-5 and an increased secretion of IFN- γ after stimulation of peripheral blood mononuclear cells with the major bee-venom allergen phospholipase A_2 (17). Probably both anergy and immune deviation are mechanisms of SIT (6).

This increased knowledge of the mechanisms of SIT has led to promising initial trials using T-cell-reactive peptides to avoid the risk of anaphylaxis (18, 19).

In conclusion, a better understanding of the mechanisms of SIT involving specific T cells and cytokines has been reached. It is still unclear how these immunologic changes are connected to the well-known clinical results of SIT. More studies are needed to explore this, and develop safer and more efficient ways to manipulate the immune system in allergic individuals with the ultimate aim of permanent cure of these diseases.

References

- Noon L. Prophylactic against hay fever. *Lancet* 1911;1:1572-1573.
- Bousquet J, Lockey RF, Malling H-J. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53 Suppl 44:1-42.
- Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157-164.
- Ebner C. Systemic immune response to specific immunotherapy. *Clin Exp Allergy* 1998;28:781-783.
- Mavroleon G. Restoration of cytokine imbalance by immunotherapy. *Clin Exp Allergy* 1998;28:917-920.
- Rolland J, O'Hehir R. Immunotherapy of allergy: anergy, deletion, and immune deviation. *Curr Opin Immunol* 1998;10:640-645.
- Smith W, Sly PD. Immunotherapy, anergy, deviation or suppression? *Clin Exp Allergy* 1998;28:911-916.
- Umetsu DT, DeKruyff RH. T_H1 and T_H2 $CD4^+$ cells in human allergic diseases. *J Allergy Clin Immunol* 1997;100:1-6.
- McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssinus* in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG and IgG subclasses. *J Allergy Clin Immunol* 1990;86:521-532.
- Østerballe O, Løwenstein H, Norm S, et al. Immunotherapy with grass pollen major allergens. Immunological results from a prospective 3-year double blind study. *Allergy* 1982;37:491-501.
- Haugaard L, Nørregaard OFH, Dahl R. In-hospital sting challenge in insect venom-allergic patients after stopping venom immunotherapy. *J Allergy Clin Immunol* 1991;87:699-702.
- Müller U, Helbling A, Bischof M. Predictive value of venom-specific IgE, IgG and IgG subclass antibodies in patients on immunotherapy with honeybee venom. *Allergy* 1989;44:412-418.
- Wierenga EA, Snoek M, de Groot C, et al. Evidence for compartmentalization of functional subsets of $CD2^+$ T lymphocytes in atopic patients. *J Immunol* 1990;144:4551-4556.
- Hosken NA, Shibuya K, Heath AW, Murphy KM, O'Garra A. The effect of antigen dose on $CD4^+$ T helper cell phenotype development in a T cell receptor-alpha beta-transgenic model. *J Exp Med* 1995;182:1579-1584.

15. Secrist H, DeKruyff RH, Umetsu DT. Interleukin 4 production by CD4+ T cells from allergic individuals is modulated by antigen concentration and antigen-presenting cell type. *J Exp Med* 1995;181:1081-1089.
16. Akdis CA, Akdis M, Blesken T, et al. Epitope-specific T cell tolerance to phospholipase A₂ in bee venom immunotherapy and recovery by IL-2 and IL-15 *in vitro*. *J Clin Invest* 1996;98:1676-1683.
17. Jutel M, Pichler WJ, Skrbic D, Urwyler A, Dahinden C, Müller U. Bee venom immunotherapy results in decrease of IL-4 and IL-5 and increase of IFN- γ secretion in specific allergen-stimulated T cell cultures. *J Immunol* 1995;154:4187-4194.
18. Müller U, Akdis CA, Fricker M, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A₂ induces specific T-cell anergy in patients allergic to bee venom. *J Allergy Clin Immunol* 1998;101:747-754.
19. Norman PS, Ohman JL Jr, Long AA, et al. Treatment of cat allergy with T cell reactive peptides. *Am J Respir Crit Care Med* 1996;154:1623-1628.