

Use of nonstimulatory peptides: A new strategy for immunotherapy?

A cynic would argue that IT for allergic diseases has changed little since its introduction by Noon 80 years ago.¹ Controlled trials in the 1960s demonstrated that IT for grass pollen or ragweed hay fever was specific and reduced symptom-medication scores and that the effect appeared to be dose related (i.e., larger allergen doses were more likely to elicit clinical improvement).² Subsequently, several approaches were used to improve IT regimens, including the use of modified immunogens (e.g., alum-precipitated extracts, allergoids, or polymerized allergens) or altering the time course or route of allergen administration (e.g., rush, nasal, or oral IT). Therapy with autologous allergen-IgG Ab "complexes" has also recently been reported.³ The rationale behind these approaches has been largely empirical: to maximize the dose of allergen administered while reducing the number of injections and, most importantly, reducing the number of adverse reactions to treatment. Although IT may alleviate symptoms of inhaled allergy (particularly for seasonal rhinitis), it is not a cure, and improved methods of IT would be welcomed. However, apart from increased IgG "blocking" Ab, which is the usual immunologic parameter associated with symptomatic improvement, the mechanisms underlying IT remain obscure. Thus, it is difficult to develop a logical strategy for improving the treatment.

An article in a recent issue of the JOURNAL by O'Hehir et al.⁴ described the use of an influenza HA peptide to inhibit T cell responses to mite allergens in vitro. The authors suggest that inhibition of the interaction between the T cell receptor and HLA class II molecules by peptides offers an alternative approach to conventional IT with allergen extracts. This approach is based on current concepts of Ag recognition by helper (CD4⁺) T cells and on recent progress in studies of the molecular biology and immune response to mite allergens. Helper T cells recognize foreign

Abbreviations used

IT:	Immunotherapy
HA:	Hemagglutinin
IL:	Interleukin
Ag:	Antigen
Ab:	Antibody

Ags that have been "processed" by macrophages and monocytes (or other Ag-presenting cells) into peptide fragments, which are then presented to the T cell receptor as a complex in the binding groove of HLA class II molecules. Triggering of the T cell receptor by peptide-HLA class II complexes on the surface of the Ag-presenting cells results in T cell activation and, ultimately, collaboration with B cells for specific Ab production.⁵ During the past 5 years, it has become possible to study the requirements for T cell recognition of inhaled allergens. Many major and minor allergens have been purified, cloned, and sequenced; allergen-specific T cell clones have been isolated; associations between allergen-specific immune responses and particular HLA-DR molecules have been identified. In previous studies, O'Hehir et al.⁶ found that a product of the HLA-DRB3 gene (DRw52b) was a dominant class II molecule used to present mite allergen to T cells. They also observed in separate studies that a 12-amino acid peptide of influenza HA (residues 307 to 319 with a serine substitution for tyrosine at position 309) bound strongly to the DRw52b molecule. Moreover, binding of this peptide analogue to DRw52b was "nonstimulatory," that is, did not result in cellular activation. The results in the current article demonstrate that the HA peptide inhibited proliferation of peripheral blood mononuclear cells to mite-allergen extract in vitro, in a dose-dependent manner, and also inhibited the proliferation of T cell clones specific for mite allergens. Proliferative responses of five mite-allergic donors and the three clones were inhibited 60% to 90% by 10 to 100 µg/ml of HA peptide. Specificity was established with a keratin peptide as a control (<10% inhibition) and by demonstrating that the HA peptide elicited no inhibition of proliferative responses to T cell activators

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(phytohemagglutinin or anti-CD3) and only partial inhibition of proliferation (13% to 40%) to a recall antigen from *Mycobacterium tuberculosis*. The authors also confirmed that the HA peptide bound to HLA DRw52b, but not to HLA DR1, by flow cytometry.

The experiments are significant because they demonstrate that T cell responses to mite allergens can be down regulated by a peptide that binds the appropriate class II molecule and because they suggest a potential new approach to IT that appears to be based on this mechanism. An obvious question is, "How does a single peptide inhibit T cell responses to multiple mite allergens in apparently unselected donors"? The answer is not completely clear, although previous work by the same group suggests that DRw52b is the class II molecule used by several mite allergen-specific T cell clones. (Unfortunately, the specificity of the clones used in the present study was not listed, although clone DE9 is known to recognize group I allergen.)⁷ The HA peptide will also bind to HLA-DRAB1 molecules, which are used to stimulate T cell responses to mite allergens (although to a lesser extent than DRw52b). In many respects these data are preliminary, and although the phenomenon is well described, it is important that the experiments be confirmed with a much larger panel of mite-allergic donors, including a more detailed analysis of the effects of the peptide on T cell responses to other protein Ags. The authors are rightly cautious about extrapolating their findings in an in vitro model system to potential effects in vivo. Even if the HA peptide can be demonstrated to modulate T cell responses in most mite-allergic patients, it would not guarantee clinical efficacy or exclude the possibilities that some patients would inevitably develop IgG and/or IgE Abs to the peptide or that beneficial immune responses, for example, to infectious agents or toxins, would be adversely affected. Nonetheless, there are several attractions to the use of peptide-based vaccines, principally, that they are well-defined chemicals that can be easily, and relatively inexpensively, produced by the pharmaceutical industry. As with other drugs, they can be chemically modified and screened for improved activity so that structural changes to the HA peptide could be envisaged that would improve its immunomodulatory effects on mite allergen-specific T cells while reducing its immunogenicity or effects on immune responses to other antigens.

Clearly, this is not the only mechanism for altering T cell responses to allergens. Several laboratories are now focusing on the identification of immunodominant T cell epitopes for inhalant allergens, and T cell clones specific for mite, cat, ragweed, and rodent allergens have been isolated. In some cases, immu-

nodominant T cell peptides have already been identified.⁸ There is also increasing evidence that clones derived from atopic individuals demonstrate different patterns of lymphokine production than clones derived from nonatopic individuals. Most T cell clones from atopic individuals appear to produce IL-4 but not interferon- γ , whereas the limited number of clones derived from nonatopic donors produce interferon- γ but not IL-4.⁹⁻¹² These studies suggest that alternative therapeutic strategies could be based either on peptides that bind the T cell receptor without causing activation, on mechanisms (as yet unclear) for down regulating Ag-specific IL-4 secreting cells, or on the induction of allergen-specific tolerance.⁸ Another useful development would be the identification of a change in T cell function or lymphokine production that correlated with symptom scores and could be used to monitor the efficacy of IT. These approaches are clearly different from Ag nonspecific mechanisms, such as peptide-based inhibition of IgE binding to the Fc ϵ receptor, which has recently again received attention.¹³

It remains to be established whether the original concept of "prophylactic" immunization against inhalant allergies, as proposed by Noon, can ever be realized. Noon believed that he was raising protective immunity to "pollen toxin," whereas IT is an attempt to down regulate an established IgE Ab response. It is certainly an interesting theoretical question as to whether the immune response to allergens could be altered by a form of immunization (e.g., parenteral or oral) before sensitization. Low-dose sensitization by inhalation of nanogram or microgram amounts of allergen each year appears to preferentially stimulate IgE Ab responses. Would high-dose immunization of unsensitized individuals result in IgG responses (perhaps mediated by a different population of T cells) without the switch to IgE Ab production or the subsequent stimulation of IgE helper cells on environmental allergen exposure? This is not entirely an academic question. It is becoming easier to predict that atopy and sensitization to allergens in infancy is associated with the development of asthma in later life.¹⁴ Prior immunization of children or unexposed adults, with markedly different immunization conditions, could potentially modify or ablate IgE responses. This is a radical approach but an approach that has been largely overlooked and perhaps deserves consideration.

With the advances in understanding of allergen-specific immune responses that have occurred in recent years, the potential applications of these studies for treatment of allergic disease should be seriously considered. The article by O'Hehir et al.⁶ provides some new ideas and has a certain historic pedigree,

coming from the same institution as Noon, and later Frankland and Augustin. The onus is now on immunologists to develop coherent strategies from which improvements in treatment can be developed.

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