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Allergen-derived T Cell Peptides and Late Asthmatic Responses

In sensitized subjects, allergen challenge can induce an early response, in the form of a wheal and flare reaction in the skin after cutaneous injection or a fall in expiratory flows after inhalation; this reaction occurs a few minutes after exposure and involves the immunoglobulin E (IgE)-mediated release of histamine and other mediators (1). In some subjects, a late asthmatic response may be observed 3 to 8 hours following allergen challenge, associated with an inflammatory process characterized by a predominance of eosinophils and activated CD4⁺ T cells, and by the production of Th2-type cytokines (2). The respective role of IgE- versus T cell-dependent mechanisms in late responses is still debated. The former is supported by observations such as the transfer of cutaneous late responses by IgE or injection of anti-IgE (3). On the other hand, a role of CD4⁺ T cells in late responses and chronic asthma has been suggested in animal models showing that airway hyperresponsiveness and eosinophilia can be adoptively transferred by CD4⁺ T cells alone following inhaled allergen challenge (4, 5).

Activation of allergen-specific T cells through peptide administration is a new way to investigate the role of the T cell in allergen-induced responses. Moreover, the possibility for peptides to modulate T cell function may lead to new therapeutic avenues. T cells possess receptors that recognize the complex of an antigenic peptide and major histocompatibility complex-encoded protein. Previous studies on human and animal T cell clones have shown that the interaction of the T cell receptor and the peptide/major histocompatibility complex protein complex can lead to either the activation or inactivation of the cell's capacity to respond to subsequent peptide or allergen challenges (6). In this regard, peptide-induced T cell tolerance is an immunologic mechanism that has been demonstrated in a variety of biological and clinical situations.

Haselden and coworkers (7) previously showed that intradermal injection of short overlapping peptides derived from chain 1 of the cat allergen *Fel d 1* that did not cross-link IgE can induce late asthmatic responses despite an absent early response. These late responses were not associated with infiltration of eosinophils or other inflammatory cells nor with an increase in concentrations of histamine and leukotrienes in bronchial biopsies or bron-

choalveolar lavage (8). This suggests that it might be possible to dissociate T cell-induced asthmatic reactions from IgE-dependent and eosinophil-dependent mechanisms in humans. With regard to the inhaled route, Hoyne and coworkers have shown that intranasal administration of a high dose of house dust mite-derived peptide in a mouse model induced a strong but transient activation of CD4⁺ cells that led to antigen-specific T cell non-responsiveness (9).

In this issue of the *Journal* (pp. 20–26), Ali and coworkers (10) address the important question of whether the reduced responsiveness to allergen observed after intradermal injection of peptides in humans may be observed when they are administered by the inhaled route (7, 8, 10). Their study shows that *Fel d 1*-derived peptides can induce an isolated late asthmatic response in cat-allergic asthmatic subjects. Contrary to what this group reported after intradermal injection, however, this late response to inhaled peptides was accompanied by eosinophilia in addition to a nonsignificant elevation of leukotrienes in the sputum. Furthermore, repeated inhalations were not associated with the abrogation of such a response. Sputum eosinophilia was similar to that observed after the first exposure and the late cutaneous response to the whole cat dander extract was not inhibited. This shows a lack of peripheral T cell tolerance that could have been conferred by inhaled peptides. The authors conclude that inhalation of the allergen-derived T cell peptides, compared with intradermal administration, is not associated with the development of hyporesponsiveness in the lung or the skin.

Although the observations reported here should be replicated because the number of subjects in the various subgroups were relatively small, they provide evidence that responses to peptides are of a different nature when inhaled compared with systemically administered. This is also quite different from the results obtained by the nasal route in rodents. The reasons for these discrepancies are uncertain although it is tempting to think that antigen-presenting cells in the skin show a different pattern of response or properties than airways cells. Furthermore, these results suggest that peptide immunotherapy may not be effective when the antigen is administered though the respiratory mucosa in humans (11). This result, in addition to studies showing modest

or no benefit of peptide immunotherapy in the treatment of cat allergy, stresses the limitations of such treatment (12, 13).

Nevertheless, the present study is a significant contribution to the debate on the role of T lymphocytes in the pathogenesis of asthma. T cell peptide-induced late responses may be secondary to T cell activation in the airways with a secondary eosinophilic response resulting from the production of cytokines such as IL-3, IL-4, IL-5, and GM-CSF or to the generation of histamine-releasing factors that activate basophils and/or mast cells to release histamine although other mechanisms may be involved (7). Furthermore, genetic determinants are considered important in the response to allergens and only certain patients seem able to react to peptides (14). Previous findings suggest that the induction of late responses results from major histocompatibility complex-restricted T cell activation (7). In this regard, the absence of late responses to peptide inhalation may well be due to a deficit in the subjects' T cell repertoire.

Future studies are needed to further explore this important field of research, particularly with regard to allergic diseases. The property of whole allergens to cross-link mast cell-bound IgE and induce the release of mediators is a limiting factor in conventional immunotherapy. The use of peptide sequences corresponding to T cell epitopes of the allergen could be an alternative with improved safety. This study by Ali and coworkers, however, is in keeping with previous clinical trials in suggesting that this form of treatment has some limitations and may not be a valuable option through the inhaled route.

Conflict of Interest Statement: L.P.B. has served as an advisor and participated in CME activities of most pharmaceutical companies involved in asthma care and to various national respiratory societies and governmental committees.

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Respiratory Epithelium in Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis Spark or Destructive Flame?

Alveolitis, as historically defined, cannot suffice as an explanation for the characteristic pattern of fibrosis and disordered lung architecture that define usual interstitial pneumonia (UIP), the morphologic counterpart of idiopathic pulmonary fibrosis (IPF). UIP/IPF remains a relentlessly progressive lung disorder despite four decades of interest in its pathogenesis and treatment. In an ATS-sponsored consensus statement it was concluded that, “we lack sufficient clinical evidence that any treatment improves survival or the quality of life for patients with IPF” (1). Despite this discouraging conclusion, the authors acknowledged the use of immunosuppressive agents as an entrenched standard of care. The rationale for immunosuppressive therapy, mainly corticosteroids, was rooted in the prevailing hypothesis that inflammation (alveolitis) was key to initiation and maintenance of lung fibrosis linked to empirical observations made at a time that precise diagnostic distinctions did not exist between IPF and its better behaved mimics.

A growing body of evidence indicates that epithelial injury and activation rather than alveolitis are almost certainly the spark responsible for a cascade of events that march inexorably toward fibrosis and honeycomb change in IPF (2). The precise steps that lie between epithelial injury and fibrosis represent a challenging puzzle into which a number of pieces have fallen. Investigators in the 1980s demonstrated features common to seemingly disparate forms of acute and chronic fibrosing lung diseases that could not easily be explained as the consequences of alveolitis (3–6). These features included epithelial necrosis, denudation and collapse of damaged epithelial basement membranes, migration of fibroblasts/myofibroblasts into air spaces, and accumulation of extracellular matrix resulting in reorganized—and in some patients restored—interstitial/intraalveolar compartments. These events were demonstrated at sites of acute lung injury in UIP/IPF (fibroblast foci), the organizing phase of diffuse alveolar damage in patients with acute interstitial pneu-