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There is continuing debate as to the relative contributions of IgE-dependent and T-cell-dependent mechanisms in the pathogenesis of the late-phase allergic reaction (LPR). On the one hand, a cutaneous LPR could be transferred by IgE, or injection of anti-IgE, while we (1), and others, have provided extensive evidence that CD4⁺ T cells are associated with the LPR and chronic asthma. Furthermore, in animal models, airway eosinophil responses and bronchial hyper-responsiveness to inhaled antigen challenge could be adoptively transferred by CD4⁺ T cells alone.

In order to provide evidence that the LPR can be provoked by T-cell activation independently of the early IgE response, we have administered peptide epitopes derived from the major cat allergen (Fel d 1) to cat-allergic asthmatics. The peptides were capable of producing T-cell proliferation but did not cross-link IgE, as shown by the basophil histamine-release assay. We hypothesized that the peptides would elicit isolated late cutaneous reactions after intradermal injection, without a preceding wheal and flare reaction. Unexpectedly, we observed that intradermal injection of the T-cell peptide epitopes produced isolated late asthmatic reactions (LAR) with no visible cutaneous response. These reactions were observed in only nine of the 45 subjects challenged. Four of the nine responders were HLA DR13 positive as compared with only one of the 31 nonreactors. The other five reactors expressed either DR1 or DR4. To confirm MHC restriction, fibroblast cell lines (FCL) transfected with HLA-DR molecules were used to present FC1P peptides of cat allergen-specific T-cell lines derived from subjects prior to peptide injection. FC1P3 (peptide 28-44 of Fel d 1 chain 1) was recognized in the context of DR13 alleles (DRB1*1301, 1302) and induced specific T-cell proliferation and IL-5 production. T cells from a DR1⁺ responder proliferated and produced IL-5 in the presence of FC1P3

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and DR1 (DRB1*0101) FCLs, whereas T cells from a DR4 + subject recognized FC1P2 (peptide 22–37) when presented by DRB1*0405. Thus, short allergen-derived peptides can directly initiate an MHC-restricted T-cell-dependent LAR, without the requirement for an early IgE/mast-cell-dependent response, in sensitized asthmatic subjects. We also observed hyporesponsiveness after subsequent rechallenge with the peptides, since repeat administration led to attenuation of the initial LAR.

Animal studies have also demonstrated an initial transient activation of T cells which precedes the development of hyporesponsiveness. Our study supports this concept, since there was abrogation of the LAR on repeat administration of the same dose of peptide which previously caused a 20% or greater fall in FEV₁. This is similar to the experience of Norman et al. (5), who also observed that there

was a progressive decline in the incidence and severity of untoward symptoms after continued treatment of cat allergy with IPC1/IPC2, suggesting that some form of tolerance may have developed after repeated administration. In addition, subjects who developed LAR in response to peptide were readministered the same dose at an interval of greater than 1 year. All developed LAR of approximately the same magnitude as that which accompanied the original challenge. These observations suggest that the induction of hyporesponsiveness after a single dose of peptide is transient, lasting somewhere between a few weeks and 1 year. Further studies are currently underway to define the precise duration of peptide-induced hyporesponsiveness in man. This may have clinical significance if repeated administration of MHC class II restricted T-cell peptide epitopes produce safe and effective long-term “tolerance”.

References

1. Haselden BM, Kay AB, Larché M. IgE-independent MHC-restricted T cell peptide epitope-induced late asthmatic reactions. *J Exp Med* 1999;**189**:1885–1894.
2. Hoyne GF, Askonas BA, Hetzel C, Thomas WR, Lamb JR. Regulation of house dust mite responses by intranasally administered peptide: transient activation of CD4 + T cells precedes the development of tolerance *in vivo*. *Int Immunol* 1996;**8**:335–342.
3. Kay AB. Concepts of allergy and hypersensitivity. In: Kay AB, editor. *Allergy and allergic diseases*. Vol. 1. Oxford: Blackwell Science, 1997:23–35.
4. Kon M, Sihra BS, Compton CH, et al. A double blind placebo controlled trial of a chimeric anti-CD4 monoclonal antibody, kleximab (IDEC CE9.1) in chronic severe asthma. *Lancet* 1998;**352**:1109–1113.
5. Norman PS, Ohman JL, Long AA, et al. Treatment of cat allergy with T cell reactive peptides. *Am J Respir Crit Care Med* 1996;**154**:1623–1638.