

A new mechanism for immunologic initiation of asthma

Allen P. Kaplan*

Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy, and Clinical Immunology, Medical University of South Carolina, Charleston, SC 29425

Nonallergic asthma (intrinsic asthma) refers to a population of asthmatics in whom there is no evidence of IgE-mediated hypersensitivity, i.e., skin tests or radioallergosorbent tests (RAST) to a wide variety of common inhalant allergens are negative (1). This form of asthma accounts for $\approx 40\%$ of adult asthmatics (but only $\approx 10\%$ of childhood asthmatics) and demonstrates histological and biochemical features that are strikingly similar to asthma that is associated with allergy. Thus, prior studies have suggested that they represent the same “immunopathologic” entity, even though the initiating mechanisms are necessarily different (2). The work by Kraneveld *et al.* (3) in this issue of PNAS demonstrates that light chains that are antigen-specific can sensitize BALB/c mice via either the cutaneous or intranasal route such that subsequent bronchial challenge with antigen can lead to release of mast cell protease 1 (mMCP-1), a measure of mast cell degranulation, mucosal exudation into the airway lumen, leukocyte accumulation in bronchoalveolar fluid, and increased airway hyperreactivity. Thus, the consequence of antigen challenge leads to all of the key features of asthma. Antigen challenge after passive administration of light chain was shown to lead to the same phenomenon. Further evidence of a requirement for mast cells was shown by performing the same experiments in mast-cell-deficient mice, which did not manifest the changes seen in the BALB/c mice, and reconstituting the response by administration of mast cells for normal littermates. The entire process was then inhibited by administration of a 9-mer peptide (F991) derived from Tam-Horsfall protein that binds (and presumably inactivates) free light chains. It should be noted that the authors’ use of the term “allergic” in the article title implies an “immunologic” mechanism that is antigen-specific and does not relate to allergic or “extrinsic” asthma where IgE-mediated hypersensitivity is requisite. It is therefore a model of the human disorder we refer to as nonallergic or intrinsic asthma.

The immunopathologic appearance of all forms of human asthma are, indeed, strikingly similar. For example, the T lymphocyte subpopulation infiltrating the lung is strongly skewed to Th2 cells (4), there is a prominent eo-

sinophilic infiltrate (sometimes associated with a blood eosinophilia), and there is a particular role for cytokines derived from Th2 cells such as IL-4, IL-5, IL-13, and IL-25 (5), plus CC chemokines (6) reactive with chemokine receptors CCR3, CCR4, and CCR8 (such as eotaxins and TARC), and to a lesser degree CXC chemokines reactive with the CXCR3 receptor (7, 8). Allergic and nonallergic asthma also share the presence of hyperresponsiveness of the bronchial smooth musculature, as demonstrated by graded inhalation of methacholine; both show evidence of “remodeling” with laying down of proteins along the

It is not obvious how antigen-specific light chains activate a mast cell to lead to an asthmatic response.

basement membrane, smooth muscle hypertrophy and hyperplasia, and development of myofibroblasts with secretion of growth factors and connective-tissue elements (9). Gradually, there can be a decrease in pulmonary function and decreased reversibility with bronchodilators. Such abnormalities are often particularly prominent in the nonallergic asthmatic population and can also be associated with resistance to the effects of corticosteroid.

The initiation mechanism for allergic asthma requires sensitization of respiratory (pulmonary) mast cells by IgE antibodies reactive with inhalant allergens such as dust mite, cockroach, pollen proteins, and mold spores. Subsequent inhalation of allergen leads to interaction of the allergenic epitopes with cell-bound IgE, so as to indirectly cross-link IgE receptors (10), followed by activation of secretory pathways to release histamine, leukotrienes C4/D4, prostaglandin D2, platelet activating factor (PAF), and a wide array of cytokines and chemokines. There is an immediate allergic response (1–20 min) with vasodilatation, an increase in vascular permeability and bronchoconstriction, followed by a slower “late-

phase” response (4–8 h) characterized by the aforementioned cellular infiltrate (Th2 lymphocytes, eosinophils, monocytes, and basophils) and a more prominent and sustained increase in bronchospasm (11) that is demonstrable even if the inciting allergen is no longer present. No such scenario can be described for nonallergic asthma because an early inflammatory phase cannot be defined, but the response described is virtually identical to the allergic late-phase response.

This study by Kraneveld *et al.* (3) raises many mechanistic possibilities that have not yet been addressed. Although the authors have previously shown that mast cells are activated in their mouse model of nonallergic asthma (12), it is not intuitively obvious how antigen-specific light chains can activate a mast cell to lead to an asthmatic response. For example, do free light chains interact with mast cells, and, if so, what membrane protein (receptor) is involved? Is dimerization of light chain a requirement so as to cross-link membrane elements? Are the mast cell signal transduction pathways activated different from those initiated by cross-linking of IgE receptors? Is there secretion of histamine, leukotriene, cytokines, and chemokines as we would anticipate in any model for asthma? If such a mechanism were operative in human nonallergic asthma, what are the allergens involved and can T or B cell reactivity to those allergens be demonstrated? The authors do add a tantalizing bit of data demonstrating that the blood level of free light chain in *both* allergic and nonallergic asthmatics is higher than is seen in normal controls or even allergic individuals who do not have asthma. There are, of course, no data to indicate that such light chains are pathogenic in man or that any antigen specificity is associated with the elevated levels they report. The requirement, however, for free light chains is emphasized by the inhibition with peptide F991, which does not interact with light chain as part of an intact Ig molecule, and they could not reproduce their data by passive infusion of the

See companion article on page 1578.

*E-mail: kaplana@musc.edu.

© 2005 by The National Academy of Sciences of the USA

IgG antibody from which the light chains were derived.

Clearly, much work is needed to explain the observations made on a molecular level and to determine whether such a mechanism is relevant to human asthma, and particularly nonallergic asthma. It is interesting to note one other report of a similar, curious induction mechanism for asthma, in this case

a human study. Intradermal injections of peptides derived from cat allergen that are reactive with T cells but not with IgE antibody result in an asthmatic response upon inhalation challenge with the antigen (13). There was no skin reactivity observed nor any histamine or leukotriene release in bronchoalveolar lavage fluids (14), indicating absence of a definable early-phase response and,

thus far, no evidence of mast-cell degranulation. A role for free light chains was not considered, but a search for such reactivity, as an alternative to a strictly T-cell-mediated event, would be of interest. It is hoped that studies such as these will lead to information that will shed light on initiating mechanisms for asthma that are immunologic but independent of IgE.

1. Ortega, D. & Busse, W. W. (1997) in *Allergy*, ed. Kaplan, A. P. (Saunders, Philadelphia), 2nd Ed., pp. 480–505.
2. Lambert, M., Durham, S. R., Ying, S., Kimmitt, P., Bakens, J., Assoufi, B., Pfister, R., Menz, G., Robinson, D. S., Kay, A. B. & Corrigan, C. J. (1996) *Am. J. Respir. Crit. Care Med.* **154**, 1497–1504.
3. Kraneveld, A. D., Kool, M., van Houwelingen, A. H., Roholl, P., Solomon, A., Postma, D. S., Nijkamp, F. P. & Redegeld, F. A. (2005) *Proc. Natl. Acad. Sci. USA* **102**, 1578–1583.
4. Larché, M., Robinson, D. S. & Kay, A. B. (2003) *J. Allergy Clin. Immunol.* **111**, 450–463.
5. Robinson, D., Hamid, Q., Bentley, A., Ying, S., Kay, A. B. & Durham, S. R. (1993) *J. Allergy Clin. Immunol.* **92**, 313–324.
6. Gonzalo, J. A., Lloyd, C. M., Wen, D., Albar, J. P., Wells, T. N. C., Proudfoot, A., Martinez, A. C., Dorf, M., Bjerke, T., Coyle, A. J. & Gutierrez-Ramos, J. C. (1998) *J. Exp. Med.* **188**, 157–167.
7. Lamkhioued, B., Renzi, P. M., Abi-Younes, S., Garcia-Zepeda, E. A., Allakhverdi, Z., Ghallar, O., Rothenberg, M. D., Luster, A. D. & Hamid, Q. (1997) *J. Immunol.* **159**, 4593–4601.
8. Liu, L., Jarpour, N. N., Busse, W. W. & Kelly, E. A. B. (2004) *Am. J. Respir. Crit. Care Med.* **169**, 1118–1124.
9. Davies, D. E., Wicks, J., Powell, R. M., Puddicombe, S. M. & Holgate, S. T. (2003) *J. Allergy Clin. Immunol.* **111**, 215–225.
10. Segal, D. M., Taurog, J. D. & Metzger, H. (1977) *Proc. Natl. Acad. Sci. USA* **74**, 2993–2997.
11. Liu, M. C., Hubbard, W. C., Proud, D., Stealey, B. A., Galli, S. J., Kagey-Sobotka, A., Blacker, E. R. & Lichtenstein, L. M. (1991) *Am. Rev. Respir. Dis.* **144**, 51–58.
12. Kraneveld, A. D., Vanderkleij, H. P. M., Kool, M., Van Houwelingen, A. H., Weitenberg, A. C. D., Redegeld, F. A. M. & Nijkamp, F. P. (2002) *J. Immunol.* **169**, 2044–2053.
13. Haselden, B. M., Kay, A. B. & Larché, M. (1999) *J. Exp. Med.* **189**, 1885–1894.
14. Haselden, B. M., Larché, M., Meng, Q., Shirley, K., Kaplan, A. P., Bates, C., Robinson, D. S., Ying, S. & Kay, A. B. (2001) *J. Allergy Clin. Immunol.* **108**, 394–402.