for deficient dendritic cell activation, restoring the responses of TLR4-deficient mice to OVA with either low- or high-dose LPS.

Conclusions. The authors concluded that inhalation of low doses of LPS with OVA antigen was necessary to induce allergic or Th2-dependent responses in the lung, whereas inhalation of high doses of LPS with antigen induced nonallergic or Th1-dependent responses. The LPS-mediated effects on allergic sensitization were dependent on signaling through TLR4 on dendritic cells.

Reviewers’ Comments. The effects of endotoxin exposure on the development of atopy and asthma are seemingly paradoxical. Although studies show that exposure to endotoxin early in life inhibits the development of asthma and atopic disease, other studies demonstrate adverse effects of endotoxin on airway function. Although endotoxin is ubiquitous in children’s environments, the exposure level can vary and may be the factor influencing the development of atopy. For example, this dosage effect may help explain the protection from atopy associated with growing up on a farm, where endotoxin exposure is excessive. The results of this study are an intriguing advance toward understanding the basis for these conflicting data, suggesting a mechanism through which the dose of endotoxin present during aeroallergen exposure could influence the incidence of allergic sensitization.

Louis A. Rosenthal, PhD
Mark H. Moss, MD
Madison, WI

ESSENTIAL ROLE OF NATURAL KILLER T CELLS PRODUCING INTERLEUKIN-4 AND INTERLEUKIN-13 IN THE DEVELOPMENT OF ALLERGEN-INDUCED AIRWAY HYPERREACTIVITY


Purpose of the Study. To determine the role of natural killer T (NKT) cells in the development of asthma.

Methods. NKT cell-deficient mice were used to determine the relative contribution of NKT cells to the development of T helper type 2 (Th2) responses and allergen-induced airway hyperreactivity (AHR).

Results. The investigators found that AHR, a cardinal feature of asthma, did not develop in the absence of NKT cells. The failure of NKT cell–deficient mice to develop AHR was not attributable to an inability of the mice to produce Th2 responses, because NKT cell-deficient mice that were immunized subcutaneously at nonmucosal sites produced normal Th2-biased responses. The failure to develop AHR could be reversed with the adoptive transfer of tetramer-purified NKT cells producing interleukin-4 and interleukin-13 to Ja281−/− mice, which lack the invariant T-cell receptor of NKT cells, or with the administration to Cd1 days−/− mice of recombinant interleukin-13, which directly affects airway smooth muscle cells.

Conclusions. Pulmonary NKT cells crucially regulate the development of asthma and Th2-biased respiratory immunity against nominal exogenous antigens. Therapies that target NKT cells may be clinically effective in limiting the development of AHR and asthma.

Reviewer’s Comments. The contribution of different cell types to the development of asthma is an area of intense interest. This elegant study points to the likely importance of NKT cells in the development of allergen-induced airway hyperreactivity, a cardinal feature of asthma.

Robert A. Wood, MD
Baltimore, MD

THE ROLE OF INTERLEUKIN-13 IN ESTABLISHED ALLERGIC AIRWAY DISEASE


Purpose of the Study. To determine the effects of blocking interleukin-13 (IL-13) on early- and late-phase airway responses in previously sensitized and challenged mice.

Study Population. Ovalbumin-sensitized and -challenged mice were studied.

Methods. Ten- to 12-week-old mice were sensitized with intraperitoneal injections of ovalbumin on days 1 and 14 and then challenged with nebulized ovalbumin for 3 days on days 28 to 30. The mice received a second challenge of nebulized ovalbumin 6 weeks after the first challenge, to assess inflammatory and histologic outcomes, airway reactivity, and early- and late-phase responses. A soluble fusion protein consisting of the extracellular domain of the high-affinity IL-13 receptor (IL-13R) and human immunoglobulin G (hIgG) (sIL-13Rα2-hlgG) was administered 24 hours and 1 hour before the second ovalbumin challenge, when early- and late-phase responses, respectively, were assessed, and was also administered 24 hours after the challenge, when inflammatory and histologic outcomes and airway reactivity at 48 hours were assessed. hlgG was administered to control mice.

Results. Levels of IL-13 in bronchoalveolar lavage (BAL) fluid were increased after the second ovalbumin challenge in previously sensitized mice, and sIL-13Rα2-hlgG significantly reduced BAL fluid levels of IL-13. The sIL-13Rα2-hlgG fusion protein also inhibited the development of the late-phase response but not the early-phase response. Airway hyperresponsiveness, assessed as changes in lung resistance and dynamic compliance after methacholine inhalation, was inhibited by sIL-13Rα2-hlgG fusion protein. sIL-13Rα2-hlgG decreased the number of cells in BAL fluid, particularly eosinophils, but did not completely eliminate them. Treatment with sIL-13Rα2-hlgG significantly reduced BAL fluid levels of IL-5 but not interferon-γ, IL-12, or IL-10.

Conclusions. IL-13 appears to play a critical role in the development of the late-phase response in previously sensitized mice. Blockade of IL-13 may be an important strategy to pursue in the development of new treatments for allergic asthma.

Reviewer’s Comments. Although this study was performed in mice, the results provide the foundation for pursuing IL-13 as a target for asthma treatment. The hope is that targeted therapy may be associated with fewer side effects than corticosteroid therapy and that treatment may be able to be tailored to specific asthma phenotypes.

Elizabeth C. Matsui, MD
Baltimore, MD

LUNG FUNCTION AND RESPIRATORY HEALTH IN ADOLESCENTS OF VERY LOW BIRTH WEIGHT


Purpose of the Study. Very low birth weight (VLBW) infants (birth weight of <1500 g) are typically preterm and usually require respiratory support in the nursery, placing them at risk for lung injury, which might have long-term consequences. Do these children have reduced lung function and respiratory disease when they reach adolescence?
ROLE OF GASTROESOPHAGEAL REFUX IN OLDER CHILDREN WITH PERSISTENT ASTHMA


Purpose of the Study. To determine the effect of gastroesophageal reflux (GER) treatment on asthma outcomes.

Study Population. Forty-six children (5–10.5 years of age) who had received treatment for moderate persistent asthma for at least 2 years and who were being cared for by a specialist were studied.

Methods. Subjects were recruited from a pulmonology practice after fulfilling the following inclusion criteria: no family history of asthma or atopy, no personal history of atopy, receiving treatment for asthma (multiple controllers) for at least 2 years, with ≥3 emergency department visits or hospitalization for treatment of asthma in the prior year, non-smoking parents, no prior history of respiratory syncytial virus bronchiolitis, and able to swallow a pill or capsule. Forty-six children were enrolled and referred to gastroenterologists, to rule out GER disease with esophageal pH (dual-channel) monitoring (for 20–24 hours). Those with abnormal pH probe study results began treatment, including lifestyle changes, prokinetic and proton pump inhibitor treatment, and, if indicated, surgical intervention. Those with normal pH study results were given the option of beginning medical treatment. The subjects were monitored at regular 4-week intervals for an 18-month period, for asthma assessment and adjustment of medications if necessary. The pulmonologist was not blinded with respect to the treatment.

Results. A total of 482 subjects were screened during a 2.5-year period. Twenty-seven of the 46 enrolled patients (59%) had abnormal pH study results, with 18 opting for medical treatment and 9 opting for surgical treatment. Of the 19 with normal pH study results, 8 opted to begin medical treatment. There were no differences in age or gender for any of the groups. The 27 patients who underwent treatment because of abnormal pH study results all were able to reduce (≈50%) the amount of asthma medication used. There was no statistical difference in outcomes between the medical and surgical intervention groups. Of those with normal pH study results, the 11 patients who did not begin GER treatment experienced no changes in their asthma medications; however, 2 of 8 patients with normal study results who began empiric GER treatment were able to reduce (70%) their requirements for bronchodilators and inhaled corticosteroids. Among patients with abnormal pH study results, the probability of improvement of asthma after GER treatment was 100%; among those with normal pH study results receiving treatment, the probability of improvement was 25%. The study found what has been shown in adult studies, that treatment of GER disease with either proton pump inhibitors or surgical intervention can improve asthma, in this case by reducing the need for rescue and controller medications. This has not been found for treatment with ranitidine. The authors found pH probe study results to be useful predictors of responses to anti-GER treatment. The study did not answer several questions, including the following. How long should medical GER treatment continue for these patients? Is the prokinetic necessary? How long will asthma improvement continue, with or without treatment? Is surgical intervention superior to medical treatment? What, if anything, in the patient history could indicate the presence or absence of GER and suggest the response to treatment? What effect does this treatment have on lung function and long-term outcomes?

Conclusions. Screening for the presence of GER disease among children with moderate persistent asthma, with pH probe studies, is a useful screening approach. Treatment of asthmatic children with aggressive acid suppression may improve asthma outcomes.

Reviewer’s Comments. Although the exclusion criteria for this study were extensive, resulting in a rather select study population, this study does demonstrate what has been found among adults, that GER disease may play a role in a significant number of asthma cases and that treatment of GER disease may lead to improvement in asthma outcomes. It also demonstrates that pH probe studies are useful screening tests for such patients, although patient histories would have been helpful in this study.

Mary Beth Bollinger, DO
Baltimore, MD

NATIONAL TRENDS IN ASTHMA VISITS AND ASTHMA PHARMACOTHERAPY, 1978–2002


Purpose of the Study. To analyze asthma clinic visits and changes in asthma (pharmaceutical) therapy during a 25-year period.

Study Population. Subject data from the National Disease and Therapeutic Index, from 1978 to 2002, were used to evaluate asthmatics examined by office-based physicians.

Methods. The National Disease and Therapeutic Index provides data on diagnostic and prescribing information.