asthma model, IL-19 levels were measured in asthmatic and control mice. To test whether IL-19 upregulates T-helper 2 (Th2) cytokines, IL-19 complementary DNA was injected into healthy mice using intramuscular electroporation, and serum levels of IL-4, IL-5, IL-10, and IL-13 were later monitored. After injection of IL-19 into asthmatic mice, IL-13 and immunoglobulin E (IgE) levels were measured. To determine if IL-19 could induce Th2 cytokine production in vitro, IL-19 was incubated with CD4+ T cells and IL-4, IL-5, IL-10, and IL-13 levels were quantified in the cell-culture supernatant.

RESULTS. Among asthmatic patients, the serum level of IL-19 was twice that of healthy controls, and those with a high level of IL-19 also had high levels of IL-4 and IL-13. In the murine asthma model, asthmatic mice also had IL-19 levels twice that of healthy control mice. Injection of the IL-19 gene into healthy mice induced production of IL-4, IL-5, and IL-10 but not IL-13. IL-19 upregulated IL-13 in asthmatic mice and also upregulated IgE production. In vitro, IL-19 was associated with increased IL-4, IL-5, IL-10, and IL-13 production by activated cells.

CONCLUSIONS. IL-19 upregulates production of Th2 cytokines in activated T cells and may be an important molecule in the pathogenesis of asthma.

REVIEWER COMMENTS. The Th2 cytokines upregulated by IL-19 play crucial roles in the pathogenesis of asthma. IL-13 regulates airway hypersensitivity and mucus hypersecretion; IL-4 is critical for IgE antibody switching; and IL-5 plays a key role in eosinophil maturation. The findings from this study suggest that IL-19 is another potentially important molecule in asthma pathogenesis and may be responsible, at least in part, for upregulation of Th2 cytokines that are critical to the development of allergic disease.

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Inflammatory Basis of Exercise-Induced Bronchoconstriction

PURPOSE OF THE STUDY. To establish whether epithelial cell and mast cell activation with release of inflammatory mediators occurs during exercise-induced bronchoconstriction (EIB) and how histamine and cysteinyl leukotriene antagonists alter the airway events occurring during EIB.

STUDY POPULATION. There were 25 patients aged 14 to 55 whose asthma was being treated only with a short-acting β2 agonist as needed and who experienced a fall in FEV1 of ≥15% after an exercise challenge.

METHODS. Induced sputum was obtained at baseline and 30 minutes after exercise challenge. In a randomized, double-blind crossover study, the cysteinyl leukotriene antagonist montelukast and antihistamine loratadine, or 2 matched placebos, were administered for 2 doses before exercise challenge.

RESULTS. The percentage of columnar epithelial cells in induced sputum at baseline was associated with the severity of EIB. After exercise challenge, histamine, tryptase, and cysteinyl leukotrienes significantly increased in the airways, and there was an increase in columnar epithelial cells in the sputum. The concentration of columnar epithelial cells was associated with the levels of histamine and cysteinyl leukotrienes. Treatment with montelukast and loratadine inhibited the release of cysteinyl leukotrienes and histamine but did not inhibit the release of columnar epithelial cells.

CONCLUSION. Epithelial cells, mast cell mediators, and eicosanoids are released into the airways during EIB, supporting an inflammatory basis for EIB.

REVIEWER COMMENTS. “Exercise-induced asthma” (EIA) is not a disease unto itself. As the authors point out, “[EIB] is a highly prevalent condition present in approximately half of patients with asthma.” Most such patients, if questioned carefully, will admit to symptoms under circumstances other than exercise, such as with upper respiratory infections or irritant or allergen exposures. It is better to consider EIB a very common phenomenon among patients with asthma. There are 2 competing hypotheses of the mechanism of EIB: (1) loss of heat leads to vascular engorgement as the airways rewarm after exercise, initiating bronchoconstriction; and (2) loss of water leads to a change in airway osmolarity that initiates epithelial cell and mast cell activation, leading to the release of inflammatory mediators in the airways that cause bronchoconstriction. These 2 theories are not necessarily mutually exclusive, and the former theory may apply more to the minority of patients who complain of symptoms only after they finish exercising (ie, when they stop breathing through an open mouth). If the number of desquamated epithelial cells before exercise is taken as an indication of the level of ongoing airway inflammation, this study would suggest that patients with worse baseline inflammation would have worse EIB. Also of note is that the combination of the cysteinyl leukotriene antagonist and antihistamine did not inhibit the desquamation. For patients in whom a short-acting β2 agonist does not prevent EIB or who have any abnormality on baseline spirometry, a truly and broadly antiinflammatory medication (ie, inhaled
corticosteroids) would seem to be the most appropriate treatment for EIB.

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Induction and Inhibition of the Th2 Phenotype Spread: Implications for Childhood Asthma


PURPOSE OF THE STUDY. T-helper 2 (Th2) phenotype spread refers to the concept that an established antigen-specific Th2 immune response may promote a Th2 response to a neoantigen. This study used a mouse model to investigate the requirements for induction and inhibition of phenotype spread to ragweed, a clinically relevant allergen.

METHODS. To induce and characterize phenotype spread, BALB/c mice were first immunized by a series of subcutaneous injections of egg ovalbumin and then challenged intranasally with ovalbumin, ragweed, or both simultaneously. Mice were finally challenged intranasally with ragweed alone to assess allergic response (Th2-mediated lung inflammation, ragweed-specific immunoglobulin E). To study the effect of time interval between the first and second antigens, the above-described experiment was repeated with ragweed being given either simultaneously with ovalbumin or 8, 24, or 48 hours after ovalbumin challenge. To investigate the role of activated Th2 cells in the induction of phenotype spread, severe combined immunodeficient (SCID) mice received ovalbumin-specific Th2 cells and naïve CD4+ T cells intravenously and were initially challenged with ovalbumin and ragweed and then challenged later with ragweed and assessed for allergic response. To evaluate whether trafficking of naïve CD4+ T cells to bronchial lymph nodes is required for the induction of phenotype spread, these cells were labeled and treated with an inhibitor of chemotaxis before the adoptive transfer experiments in the SCID mice. The effect on phenotype spread of immunostimulatory sequence-oligodeoxynucleotide (ISS-ODN), a Toll-like receptor 9 (TLR9) agonist, was first assessed in BALB/c mice by using the protocol described above, with injection of ISS-ODN before intranasal ovalbumin and ragweed challenge. ISS-ODN was also tested in the SCID adoptive-transfer model to study its effect on trafficking to regional lymph nodes.

RESULTS. The experiments yielded the following results: (1) Th2 phenotype spread to the neoallergen (ragweed) was induced only within the first 8 hours after bronchial challenge with the first antigen (ovalbumin); (2) the differentiation of naïve CD4+ T cells to Th2 cells required trafficking of naïve CD4+ T cells to bronchial lymph nodes and required interleukin-4 produced by ovalbumin-activated Th2 cells; and (3) a TLR9 agonist inhibited phenotype spread and experimental asthma by decreasing the production of chemokines involved in the trafficking of activated Th2 and naïve CD4+ T cells to regional lymph nodes.

CONCLUSIONS. Th2 phenotype spread is the mechanism by which allergic sensitization to inhaled allergens is expanded in an already Th2-primed host. It occurs in regional lymph nodes and is mediated by interleukin-4 produced by activated Th2 cells.

REVIEWER COMMENTS. Studies have suggested that initial exposure to aeroallergens, the development of Th2 memory against them, and the associated clinical allergic manifestations occur during early childhood. Th2 phenotype spread may be the mechanism by which the allergic/asthmatic phenotype develops in early childhood. This study offers an animal model for further study of the inhibition of Th2 phenotype spread, which may lend insight to immunomodulatory interventions that could curb phenotype spread in early childhood, thereby attenuating or halting the allergic march.

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Self-Organized Patchiness in Asthma as a Prelude to Catastrophic Shifts


PURPOSE OF THE STUDY. To reveal self-organized small airway constriction contributing to large ventilation defects in asthmatics.

STUDY POPULATION. Mild and moderate asthmatics.

METHODS. Ventilation defects in asthmatics were studied during methacholine bronchoprovocation by using serial dynamic positron emission tomography with a positron-emitter nitrogen-13 tracer and a single terminal-airway model.

RESULTS. Heterogeneity of ventilation defects in asthmatics was demonstrated. In this model, constriction of terminal bronchioles was the main feature of bronchoconstriction, contributing to nonuniform ventilation defects. Consequently, on the basis of the mechanical interdependence in expansion between airways and surrounding parenchyma, clusters of constricted terminal bronchioles fed by a common tree branch developed and led to large ventilation defects.
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