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 naive 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 naive 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 naive CD4\(^+\) T cells to Th2 cells required trafficking of naive 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 naive 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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