

though its pathogenesis is still unclear, VEGF (an inducer of angiogenesis) recently attracted considerable attention as a major contributor to airway remodeling. VEGF was first discovered as a vascular permeability factor >20 years ago. Subsequently, it was revealed to be a potent inducer of endothelial cell activation and growth. Overexpression of VEGF and its receptor in the airways has been demonstrated in stable asthma and during asthma exacerbations and are reduced by conventional asthma therapies (ie, inhaled corticosteroids and leukotriene receptor antagonists). The findings of this study imply an essential role of VEGF in asthma pathogenesis with links to Th2-mediated airway inflammation and remodeling. The results of this study may also inform the link of respiratory syncytial virus infection and asthma development in children, because respiratory syncytial virus up-regulates VEGF production. This disclosed role of VEGF highlights a potential therapeutic role for a VEGF receptor antagonist in asthma.

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#### **VIRAL-INDUCED T HELPER TYPE 1 RESPONSES ENHANCE ALLERGIC DISEASE BY EFFECTS ON LUNG DENDRITIC CELLS**

**Dahl ME, Dabbagh K, Liggitt D, Kim S, Lewis DB. *Nat Immunol.* 2004;5:337-343**

*Purpose of the Study.* To determine the role of interferon (IFN)- $\gamma$  and dendritic cells in allergic pulmonary disease after influenza A infection.

*Study Population.* IFN- $\gamma$  knockout and wild-type mice completely recovered from influenza A infection were studied.

*Methods.* Mice were inoculated intranasally with influenza A virus. The postinfluenza mice were then sensitized and challenged with allergen. Airway inflammatory cells, specific antibody responses, and pulmonary dendritic cell functions were examined. In some of the wild-type mice, a neutralizing IFN- $\gamma$  monoclonal antibody was administered repeatedly after the viral inoculation.

*Result.* Pulmonary dendritic cells of postinfluenza mice enhanced allergen-specific T-helper (Th)2 responses via an IFN- $\gamma$ -dependent mechanism.

*Conclusion.* The Th1 immune response caused by an influenza infection perpetuates Th2-dependent allergic asthma by altering pulmonary dendritic cell function.

*Reviewers' Comments.* The role of respiratory viral infections in the development of allergen sensitization and asthma has been perplexing. Acute viral respiratory tract infections are the primary cause of asthma exacerbations in children and adults; however, the influence of viral respiratory infections on subsequent allergic sensitization and disease in young children is unclear. Viral infections are simplistically thought to augment Th1 (interleukin [IL]-12 and IFN- $\gamma$ ) responses and, as a result, antagonize Th2 (IL-4, IL-5, and IL-13) responses and decrease the risk of developing atopic diseases and asthma (ie, the hygiene hypothesis). Based on mouse models of allergic asthma, the impact of influenza infection on Th2 development and allergen sensitization has resulted in both beneficial and detrimental outcomes. The factors accounting for the different results are likely to be differences in experimental methods, including the timing of infections relative to allergen sensitization, the type and dose of allergen used, and the strain of the mouse. The findings of the Dahl et al study indicate that a preceding influenza infection with

subsequent Th1 immune responses can amplify subsequent Th2 immunity. Thus, the Th1-Th2 paradigm of mutual exclusivity (ie, Th1 inhibits Th2, and vice versa) seems to be overly simplistic in the circumstance in which Th1 begets Th2. Although the result of the study has not been observed or correlated in humans, the finding may provide a mechanistic explanation for a recent report of the increased risk of asthma/reactive airways disease in young children <36 months of age who received a live attenuated intranasal influenza vaccine (published by Bergen et al in *Pediatr Infect Dis J.* 2004;23:138-144).

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#### **RELATION OF CD4+CD25+ REGULATORY T-CELL SUPPRESSION OF ALLERGEN-DRIVEN T-CELL ACTIVATION TO ATOPIC STATUS AND EXPRESSION OF ALLERGIC DISEASE**

**Ling EM, Smith T, Nguyen XD, et al. *Lancet.* 2004;363:608-615**

*Purpose of the Study.* The investigators proposed to determine if the amount of inhibition of allergic responses by CD4+CD25+ T cells was related to atopy and allergic disease.

*Study Population.* Volunteers who were atopic ( $n = 12$ ) or nonatopic ( $n = 9$ ) or had hay fever ( $n = 11$ ) were recruited by advertisement and from among hospital staff and allergy clinic patients.

*Methods.* Cells were isolated from atopic donors (positive serum-specific IgE or skin tests and a history of allergic symptoms), nonatopic donors (no history of allergic symptoms, negative skin-prick tests, and normal amounts of serum IgE), and patients with hay fever (rhinitis symptoms between June and August and positive skin-prick tests to grass pollen extract but not to other allergens). Peripheral blood mononuclear cells (PBMCs), CD4+CD25+ T cells, CD4+CD25- T cells, and 2:1 ratios of CD4+CD25- and CD4+CD25+ T cells were cultured for 6 days with cat dander, grass pollen, or medium alone (negative control). The supernatant was analyzed for cytokines, and incorporation of <sup>3</sup>H-thymidine was used as an index of proliferation.

*Results.* In allergen-driven cultures, CD4+CD25+ T cells from nonatopic donors showed little proliferation and suppressed CD4+CD25- T cell proliferation in a dose-dependent manner. CD4+CD25- T cells showed enhanced production of interleukin (IL)-5 compared with unseparated PBMCs ( $P = .0056$ ). Compared with nonatopic individuals, suppression of allergen-driven proliferation of CD4+CD25- T cells by CD4+CD25+ T cells was lower in atopic patients ( $P = .012$ ) and lowest in patients with hay fever who had active rhinitis ( $P = .0003$ ). Suppression of IL-5 production was also lowest in patients with hay fever who had active rhinitis ( $P = .0166$ ). When the patients with hay fever were studied outside of their allergy season, the suppression of proliferation was greater than during their allergy season but less than in nonatopic individuals ( $P = .0028$ ) and similar to the atopic group.

*Conclusions.* In atopic individuals, especially those with active rhinitis symptoms, CD4+CD25+ regulatory T cells showed a decreased ability to regulate allergen-driven responses, compared with nonatopic individuals.

*Reviewers' Comments.* In vitro, the decreased suppression of allergen-driven responses by CD4+CD25+ regulatory T cells from atopic individuals supports the associa-

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*Pediatrics* 2005;116;557

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