Purpose of the Study. To determine if long-term exposure to air pollution adversely affects the growth of lung function during rapid lung development and if it has clinically significant adverse effects on final lung function attained during adolescence.

Study Population. Fourth-grade children (average age: 10 years) were enrolled and followed prospectively for 8 years.

Methods. Fourth-grade children (n = 1759) were recruited from elementary schools in 12 communities of southern California. Spirometric data were attained annually for 8 years. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and midexpiratory flow rate were evaluated. The attrition rate of subjects was ~10% of subjects per year. Air pollution–monitoring stations were set up in the 12 study communities to measure exposures to ozone, acid vapor, nitrogen dioxide, particulate matter, elemental carbon, and organic carbon. Linear regression was used to examine the relationship of air pollution to the FEV1 and other spirometric measures.

Results. Over the 8-year period, deficits in the growth of FEV1 were associated with exposure to nitrogen dioxide (P = .005), acid vapor (P = .004), particulate matter with an aerodynamic diameter of <2.5 μm (PM2.5) (P = .04), and elemental carbon (P = .007) even after adjustment for several potential confounders and effect modifiers. Associations were also observed for other spirometric measures. Exposure to pollutants was associated with clinically and statistically significant deficits in the FEV1 attained at the age of 18 years. For example, the estimated proportion of 18-year-old subjects with a low FEV1 (defined as a ratio of observed to expected FEV1 of <80%) was 4.9 times as great at the highest level of exposure to PM2.5 as at the lowest level of exposure (7.9% vs 1.6%; P = .002). Exposure to ozone was not proven to be a contributor to lung-function deficit.

Conclusions. The results of this study indicate that current levels of air pollution in the communities evaluated have chronic, adverse effects on lung development in children from the age of 10 to 18 years. This long-term exposure leads to clinically significant deficits in attained FEV1 as children reach adulthood.

Reviewers’ Comments. This prospective study illustrates that chronic exposure to particular air pollutants negatively impacts the progression of lung function. From a public health perspective, it is important to consider and ameliorate environmental exposures that can have an adverse effect on final attainment of lung function.

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CHARACTERIZATION OF A COMMON SUSCEPTIBILITY LOCUS FOR ASTHMA-RELATED TRAITS


Purpose of the Study. Susceptibility to asthma is known to be hereditary, but the specific genes that determine the risk for asthma are not understood completely.

Study Population. The initial studies were conducted on a geographically isolated cohort in northern Finland, and the genetic associations were then confirmed in a separate cohort from Quebec. Finally, a mouse model of ovalbumin-induced lung inflammation was used to address mechanistic questions.

Methods and Results. Positional cloning was used to identify a 133-kilobase segment containing 2 genes that were associated with asthma risk and high IgE. One of these genes coded for a G protein-coupled receptor named G protein-coupled receptor for asthma susceptibility (GPRA); the B isoform of this protein was found to be elevated in bronchial biopsies and smooth muscle from asthmatic individuals. Lung tissue of sensitized mice also expressed higher levels of GPRA mRNA.

Conclusions. Together, these data implicate GPRA in the pathogenesis of atopy and asthma and provide a novel therapeutic target for these disorders.


Purpose of the Study. To evaluate the role of vascular endothelial growth factor (VEGF) in T-helper type 2 (Th2) cell-mediated airway inflammation.

Study Population. Lung-targeted VEGF165 transgenic mice and wild-type mice.

Methods. Phenotypes of transgenic mice with elevated VEGF induced by doxycycline were studied and compared with wild-type mice. Airway histologic and physiologic assessments with special stains of microvasculatures, epithelium cells, inflammatory cells, smooth muscle cells, and dendritic cells (DCs) as well as allergen sensitization and methacholine tests were performed.

Results. Both Th2 and epithelial cells were primary sources of VEGF. Mice with overexpressed VEGF in the airways demonstrated increased neovascularization, mucous gland metaplasia, edema, collagen deposition, myocyte hyperplasia with enlarged smooth muscle bundles, inflammatory cells, activated DCs, airway hyperresponsiveness, interleukin 13 mRNA expression, Th2 responses, and allergen sensitization.

Conclusions. VEGF is a potent mediator of allergic airway inflammation by enhancing allergen sensitization, airway hyperresponsiveness, Th2 inflammation, and airway remodeling.

Reviewers’ Comments. Well-described airway pathology in asthma includes epithelial desquamation, goblet cell hyperplasia, collagen deposition below the basement membrane, smooth muscle hypertrophy/hyperplasia, and the growth and proliferation of new blood vessels. Al-
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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RELATION OF CD4+CD25+ REGULATORY T-CELL SUPPRESSION OF ALLERGEN-DRIVEN T-CELL ACTIVATION TO ATOPIC STATUS AND EXPRESSION OF ALLERGIC DISEASE


**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 (rhiinosis 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 3H-thymidine was used as an index of proliferation.

**Results.** In atopic-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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