Evolution of immunologic changes during allergen immunotherapy

Immunotherapy works by tolerizing patients with injections of allergen in gradually increasing doses. This therapy induces production of the anti-inflammatory cytokine IL-10 by T cells as well as allergen-specific IgG4 antibodies that antagonize some of the effects of IgE. In vitro, IL-10 is a cofactor for the production of IgG4 by B cells. Immunotherapy also inhibits the early- and late-phase cutaneous responses to intradermal allergen provocation. The timeframe of induction of these immunologic and clinical markers during desensitization has never been accurately defined, even though this is important for understanding the processes that can lead to reintroduction of clinical tolerance to allergen. Francis and coauthors (p 1120) have examined these parameters in a placebo-controlled study of grass pollen immunotherapy for seasonal allergic rhinitis. They report that IL-10 production and late response suppression appear to be early events, occurring within 2 to 4 weeks of a conventional 8-week updosing protocol. In contrast, the changes in antibodies and suppression of early responses became significant later, at 6-12 weeks, at allergen doses more usually associated with clinical efficacy (see Figure). The authors conclude that antibody responses may be necessary for clinical protection but that the early IL-10 production could contribute to this process.

Induced nasal allergic inflammation leads to simultaneous maxillary sinus eosinophilia

To explore the relationship between allergic rhinitis and chronic rhinosinusitis, Baroody et al (p 1126) investigated the effect of nasal allergen challenge on inflammation within the maxillary sinus. They pretreated 20 seasonal allergic subjects out of season with either loratadine (10 mg by mouth daily) or placebo for 1 week in a blinded, crossover study. They then performed a nasal allergen challenge and monitored inflammation in lavages of both the nasal cavity and the ipsilateral maxillary sinus. Eleven of the subjects underwent a similar challenge with lactated Ringer's solution as control. Compared with the lactated Ringer's solution challenge, allergen challenge resulted in a significant nasal inflammatory response (see Figure). More importantly, there was a significant increase in comparison with control in maxillary sinus eosinophils and levels of albumin and histamine during the late response. Loratadine resulted in significant inhibition of the nasal early response, with no effect on the late response in the nose or sinus. This study suggests that a neural reflex or systemic allergic inflammation creates an inflammatory response in the maxillary sinuses during allergic rhinitis and may explain the clinical relationship between allergic rhinitis and chronic rhinosinusitis. Future research will be directed at the mechanisms underlying this observation and whether or not it occurs during natural exposure.

Impact of air pollution on inner-city children with asthma

Asthmatic children in inner-city communities may be particularly vulnerable to adverse effects of air pollution because of their airways disease and exposure to relatively high levels of motor vehicle emissions. O'Connor et al (p 1133) investigated the association between short-term fluctuations in air pollution and asthma morbidity among inner-city asthmatic children. They analyzed data from 861 children with persistent asthma in 7 US urban communities who performed 2-week periods of twice-daily pulmonary function testing every 6 months for 2 years. Asthma symptom data were collected every 2 months. Daily pollution measurements, obtained from the Environmental Protection Agency's Aerometric Information Retrieval System, were almost all below the National Ambient Air Quality Standards (NAAQS). Higher concentrations of nitrogen dioxide (NO₂), sulfur dioxide, and particles smaller than 2.5 μm (PM₂.₅) were associated with significantly lower pulmonary function. Higher NO₂ and PM₂.₅ concentrations were associated with asthma-related missed school days, and higher NO₂ concentrations were associated with asthma symptoms. The investigators concluded that among inner-city asthmatic children, increases in air pollution, even below the NAAQS, were associated with adverse respiratory health effects. The associations with NO₂ suggest that motor vehicle emissions may be causing excess morbidity in this population.
Surfactant protein D–dependent innate immunity influences atopy and asthma

In addition to preventing airway collapse by lowering surface tension, pulmonary surfactant represents a natural barrier against inhaled pathogens. A polymorphism altering a single amino acid (replacing a Methionine by a Threonine at position 11) is known to affect the ability of surfactant protein D (SP-D) to bind pathogens and efficiently clear infections. Brandt et al (p 1140) have demonstrated that this polymorphism is associated with a lower susceptibility to develop atopy (in African Americans) and potentially also asthma. Furthermore, they pursued a similar line of research in mice by demonstrating that SP-D deficiency results in increased pulmonary inflammation characterized by increased cellular infiltrate—notably, neutrophils and CD4^+ T cells (see Figure)—probably resulting from exposure to endotoxins. The authors show that SP-D–deficient mice have an impaired ability to mount TH2 immune responses. Indeed, these mice have lower eosinophil levels as well as abrogated airway resistance following repeated intranasal exposures to *Aspergillus fumigatus*. Taken together, these results support the hypothesis that SP-D–mediated innate immunity influences allergen-induced adaptive immunity.

First functional characterization of the allergy-associated gene, *PHF11*

Whole-genome genetic screens using DNA chip-based technologies will accelerate the discovery of allergy-associated genes, and the challenge facing researchers is to ensure that genetic studies are accompanied by timely functional studies. In this issue, Clarke et al (p 1148) describe the function of *PHF11*, a novel gene first associated with asthma and total IgE and later with childhood atopic dermatitis. The work of these authors, using primary human T cells and siRNA knockdown technology, shows that *PHF11* is preferentially expressed in T_{H1} relative to T_{H2} cells (see Figure) and regulates gene transcription through the nuclear factor-κB pathway. Polymorphisms associated with childhood atopic dermatitis confer reduced expression of *PHF11* in T_{H1} cells, and knockdown of *PHF11* gene expression decreases the expression of the T_{H1} cytokine IFN-γ. It has long been known that T_{H1} cells in atopic children show a slower maturation than those in nonatopic children and that this contributes to early atopic sensitization and later severity of allergic disease. Clearly, genetic control of *PHF11* is only one part of this complex story, and much remains to be done to fully understand the function of this gene; however, the results of Clarke et al suggest a link between the development of T_{H1} cells and the genetics of allergy.

Rhinovirus infection results in priming of epithelial cells for T-cell interaction

Although viral infections are an important trigger of exacerbations of chronic rhinosinusitis and asthma, the mechanism by which this occurs is unclear. As reported in this issue, Heinecke et al (p 1155) have found rhinovirus-induced expression on airway epithelium of members of the B7 homolog family of costimulatory molecules, which are important T cell–interacting ligands. These results were observed in human airway epithelial cells both in vitro and in vivo. In vitro exposure of human primary bronchial epithelial cells (PBEC) or primary nasal epithelial cells (PNEC) to rhinovirus resulted in selective induction of cell-surface expression of the putative inhibitory costimulatory molecules, B7-H1 and B7-DC. These results were reproduced when double-stranded RNA, an intermediate in viral replication, was used as a stimulus. In addition, in vivo experimental rhinovirus infection of human subjects resulted in selective induction of B7-H1 and B7-DC mRNA from nasal epithelial cell when examined at the time of peak symptom scores. These studies demonstrate that human rhinovirus infection results in priming of the epithelium for potential interaction with T cells that are known to be abundantly present within diseased airways. This presents a novel mechanism by which innate immune triggers may modulate adaptive immune responses in the pathogenesis of chronic rhinosinusitis and asthma.