

Can Specific IgE Discriminate between Intrinsic and Atopic Asthma?

One of the interesting conundrums in asthma research is that some individuals appear to be susceptible to allergic triggers and others less so. This distinction led to the definition of atopic asthma and intrinsic (or nonatopic) asthma. Although many studies have examined these two groups, it is unclear what the differences are in underlying mechanisms between them (1). It is into these murky waters that Mouthuy and colleagues (pp. 206) ventured in this issue of the *Journal* (2).

On the basis of studies of rhinitis in which local antigen-specific IgE can be identified in the absence of any systemic-specific IgE, the authors hypothesized that individuals with intrinsic asthma might be similar to patients with nonallergic rhinitis with “entopy”—the presence of antigen-specific IgE in local mucosal tissues (in this case, lung rather than nasal tissues) without any evidence of systemic antigen-specific IgE (3, 4). This would then explain why the patients with intrinsic asthma have negative skin tests against relevant allergens. To test this hypothesis the authors enrolled subjects with asthma who were either skin test positive to dust mite (atopic asthma) or skin test negative (intrinsic asthma). Using sputum as a marker for mucosal airway tissue, they then measured the amount of total and allergen-specific IgE in the sputum of subjects with asthma and normal control subjects. Interestingly, subjects with intrinsic or atopic asthma were indistinguishable in terms of total and dust mite–specific IgE, with both of these groups having greater sputum IgE levels than those seen in healthy subjects without allergy.

Even though both intrinsic and atopic subjects had similar levels of dust mite–specific IgE in sputum, only atopic subjects responded to whole lung allergen challenge with a decrease in FEV₁. This is in contrast to the patients with nonallergic rhinitis where “entopy” often leads to disease upon local challenge (4). In many ways the data from the current report highlight the difference between sensitization and allergic disease. The ability to make IgE (sensitization) does not equate with atopic disease, as a significant proportion of the population can be found to have systemic and mucosal antigen–specific IgE but remain asymptomatic upon exposure to the relevant allergens. This is a particularly important issue with food allergies, as many people have specific IgE against foods that they tolerate daily without symptoms (5).

In the article by Mouthuy and coworkers, the authors attempted to determine a potential mechanism for the failure of allergen challenge in subjects with intrinsic asthma to lead to a decreased FEV₁. In particular, they focused on the ability of dust mite allergen to activate basophils from either intrinsic or atopic asthma donors, when cultured with sputum from these subjects. Interestingly, only when basophils came from subjects with atopic asthma did the addition of dust mite allergen lead to activation of the cells. These intriguing data support the contention that the difference between subjects with intrinsic and atopic asthma exists at the threshold at which their basophils activate. Whether this difference also applies to a subject’s mast cells is unknown, but it would be reasonable to consider given the two groups’ difference in skin test reactivity.

The current study is not without its limitations. One issue is the use of sputum, which may not faithfully replicate the mucosal secretions of the lower airways. It may be that subjects with intrinsic asthma and patients with nonallergic rhinitis make significant amounts of allergen-specific IgE only in the upper airways, and this is why there was no drop in FEV₁ with allergen challenge. Another issue is the fact that the differences in allergen-

specific IgE were only identified for dust mite allergen, and not for other allergens. In fact, the authors found specific IgE in the sputum from all subjects (including normal control subjects) against cat and grass. These findings do raise concern over the specificity of this response, as well as the sensitivity of the tests used to measure specific IgE. Further, although not the major focus of the study, the basophil studies utilized a rather small number of subjects, and no evidence was provided regarding the relative density of the high-affinity receptor for IgE (FcεRI) on basophils in subjects with intrinsic and atopic asthma—something that can clearly alter the activation of these cells (6).

Nonetheless, the current study does begin to illuminate potential differences between atopic and intrinsic asthma. It is interesting to speculate that atopic individuals have a lower set-point for activation of their basophils and possibly mast cells. Perhaps to understand this we need to understand better the potential role of IgE, and why IgE is made against antigens. It may be that the IgE is really a component of the mucosal immune response against any nonbacterial exposure. Recent studies in mice have shown that IgE is produced during viral infections—both IgE specific for the virus and IgE against environmental allergens (7, 8). This work has suggested that IgE is part of the antiviral response, and that atopic disease may be a sequela of this antiviral immune response. While controversial, evidence does exist in the literature that humans make IgE against viruses as well (9–14). In fact, a recent study showed that treatment with anti-IgE prevented both environmental and seasonal viral-induced exacerbations in children with asthma, suggesting that antiviral IgE may be important in asthma exacerbations (15). These data, in conjunction with the findings in the current report, suggest that local IgE production against allergens occurs in most individuals, with systemic responses only in those destined to become atopic.

In summary, the current report by Mouthuy and colleagues begins to unravel the potential mechanisms that may underlie some of the disparate phenotypes seen in patients with asthma (2). The difference between making IgE (sensitization) and development of allergic disease may well underlie these findings, and underscore the importance of not relying solely on the presence or absence of IgE as an indicator of atopic disease. Whether defects in basophil activation ultimately are responsible for the apparent lack of atopic disease in subjects with intrinsic asthma must await more detailed studies.

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Endothelial Chronic Destructive Pulmonary Disease (E-CDPD): Is Endothelial Apoptosis a Subphenotype or Prequel to COPD?

In this issue of the *Journal*, Gordon and coworkers (pp. 224) present the very interesting finding that smokers exhibit pulmonary endothelial injury and apoptosis, even in the absence of obvious radiographic, spirometric, or clinical evidence of emphysema or airflow obstruction (1). The extent of endothelial damage is greatest in smokers with isolated reductions in DL_{CO}, suggesting that this process is central to impaired lung gas exchange. They report that smokers have increased levels of circulating endothelial micro-particles (CD42b⁺CD31⁺), which demonstrate an apoptotic phenotype (reduced CD42b⁺CD62⁺/CD42b⁺CD31⁺ ratio and increased annexin V⁺ expression), and appear to originate from the pulmonary vasculature (evident by positive immunostaining for angiotensin-converting enzyme). They replicate these findings in two unrelated patient cohorts exposed to cigarette smoke, including one with HIV infection. This study raises interesting questions about the early evolution of smoking-related lung disease, and suggests that vascular and emphysematous subphenotypes of chronic obstructive pulmonary disease (COPD) exist, possibly pathologically determined by primary cellular apoptosis and tissue destruction (Figure 1). From a practical clinical standpoint, the work highlights the limitations of the GOLD guidelines and the FEV₁ as a summary measure for the diagnosis and staging of COPD.

The role of pulmonary microvascular “atrophy” in the pathogenesis of emphysema has been considered for over half a century, after pathologists noted that there was a paucity of blood vessels in lung parenchyma with emphysema (2). While the role of the protease/antiprotease balance and inflammatory cells, such as neutrophils, macrophages, and T lymphocytes, in lung

tissue destruction has been studied extensively (3–5), only during the last decade have investigators started to re-examine the specific role of pulmonary endothelial cell injury and dysfunction in disease pathogenesis.

In 2000, Kasahara and colleagues demonstrated that inhibition of vascular endothelial growth factor (VEGF), a tropic factor required for endothelial cell survival, leads to development of emphysema in rats (6). In human lungs where emphysema had already developed, they found that VEGF, VEGF R2, and mRNA levels were reduced (7). The current study by Gordon and colleagues adds to these findings by demonstrating that pulmonary endothelial cell apoptosis may be an early event, apparently developing in the lungs of smokers who have no radiographic evidence of emphysema. The identification of elevated levels of microparticles does not necessarily define endothelial cell apoptosis as the trigger event in the development of emphysema, as it is possible that a primary process arising from the epithelium or matrix could lead to endothelial cell apoptosis in the associated vasculature. However, it is intriguing to speculate that the endothelial cell may be uniquely susceptible or more sensitive to toxins generated from cigarette smoking. Smoking-mediated endothelial dysfunction is characterized by an imbalance of nitric oxide and reactive oxygen species formation, up-regulation of stress response pathways, and pathological expression of adhesion molecules (8). According to an endothelial origin of disease model, primary endothelial activation then drives neutrophil recruitment with secondary neutrophil elastase-dependent inflammation, matrix destruction, and alveolar dropout.

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