

Neosensitization to Allergens after Resolution of Allergic Airways Inflammation A New Role for Airway Dendritic Cells

In people suffering from allergies, sensitization to additional “new” allergens over time is common. Such neosensitization not only happens in allergic rhinitis and asthma, but also in eczema and food allergies. Strong sensitization, as measured by high allergen-specific IgE levels, particularly at an early age, increases the probability of a child developing sensitizations to additional aeroallergens (1). The likelihood of clinical manifestation of allergic asthma, allergic eczema, and allergic rhinitis has been shown to rise as the range of allergic sensitizations increases (2). Therapeutic induction of tolerance toward an allergen can reduce the likelihood of neosensitization (3, 4), which may therefore reduce associated progression of allergic disease. However, there is a need for further understanding of when and how neosensitization occurs. So far, neosensitization to allergens has been ascribed to collateral priming, the induction of a Th2 response toward a “new” allergen that is encountered at a time when another “known” allergen triggers Th2 responses (5, 6).

In this issue of the *Journal*, van Rijt and colleagues (pp. 303) report their novel and intriguing observation of an enhanced capacity for neosensitization via the airways, well after the resolution of allergic airways inflammation (7). The study utilizes a mouse model of severe eosinophilic airways inflammation, induced by repeated prolonged intratracheal challenges with “unpulsed” bone marrow–derived dendritic cells (DCs), which present medium-derived fetal calf serum antigens. One month after the end of DC challenges, when airway eosinophilia and goblet cell hyperplasia had resolved but airway remodeling persisted, “post-inflammation” mice were exposed to a single dose of the model allergen ovalbumin (OVA) without adjuvant. Mice were then challenged with OVA aerosol 2 weeks later. Post-inflammation mice, but not controls without previous airways inflammation, developed new allergic airways inflammation with eosinophil influx, goblet cell hyperplasia, and OVA-specific IgE antibodies in serum. Furthermore, in post-inflammation mice, adoptively transferred naïve OVA-specific T cells were shown to undergo Th2 differentiation following OVA challenge, a response not seen in controls. Importantly, airway DCs from post-inflammation mice expressed higher levels than controls of the co-stimulatory molecules CD80, CD86, CD40 and the adhesion molecule ICAM-1. They also had increased RNA expression of Ym1/2, a marker of alternative activation in macrophages, and of the co-stimulatory molecule OX40 ligand, both of which have been implicated in promoting Th2 responses (8, 9). *In vitro* these DCs were shown to be sufficient for the induction of proliferation and Th2 cytokine production in naïve OVA-specific T cells. Hence, the DCs present in the lung following the resolution of allergic airways inflammation, but where airways remodeling was evident, were in a functional state that preferentially induced Th2 responses, and were presumably sufficient for neosensitization. Previous work by the same group that showed a requirement for airway DCs for allergic sensitization

via the airways and for the development and maintenance of allergic airways inflammation (10), suggests that these Th2-promoting DCs are also likely to be necessary for neosensitization after the resolution of inflammation.

The findings of van Rijt and colleagues that mature lung DCs persisted a month after the end of allergen challenges seemed surprising, since activated DCs in ongoing allergic inflammation migrate to the regional lymph nodes, have a short life span, and are usually replaced by immature DCs (11). However, similar observations of long-term persistence of activated lung DCs have been made in models of respiratory viral infection; in mice infected with respiratory syncytial virus (RSV) numbers of mature lung myeloid DCs remain elevated for several weeks beyond the resolution of disease and inflammation (12, 13). Children with RSV infection have increased numbers of DCs in their nasal mucosa, and these increase even further after the resolution of infection (14). Thus, the observations reported here, and in virus-induced respiratory inflammation, raise the interesting question as to what factors support the long-lasting activation of lung mDCs after acute airway inflammation has resolved. As discussed in the article by van Rijt and colleagues, prime candidates include effects mediated by altered extracellular matrix and by cells involved in airway remodeling such as myofibrocytes, myocytes, and epithelial cells. In addition, factors that promote the Th2-polarizing capacity of DCs, such as IL-33 or TSLP (15, 16), could also be implicated, and warrant further study. It would also be important to know whether prolonged DC activation and enhanced neosensitization is only found after severe and prolonged allergic inflammation with features of remodeling, as seen in the model used by van Rijt and colleagues, or if this can also occur independently of remodeling and following short-term airway inflammation, as would be envisaged in virus-induced asthma exacerbations.

The important observation made by van Rijt and colleagues that following the resolution of allergic inflammation, persisting mature airway DCs facilitate neosensitization, may have important clinical implications, and clinical studies are warranted. Studies of airway DCs following the resolution of seasonal asthma could determine if long-term activation of these cells also occurs in humans. In addition, it would also be important to explore whether similar phenomena occur in other organs, in particular the skin. Finally, detailed clinical studies with serial assessments of allergic sensitization may help increase our understanding of the timing of neosensitization in relation to exacerbations of allergic inflammation.

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JÜRGEN SCHWARZE, M.D.

KAREN J. MACKENZIE, M.B.Ch.B., B.Sc.

MRC Centre for Inflammation Research, and Child Life and Health

University of Edinburgh
Edinburgh, United Kingdom

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To Use or Not to Use Clinical Decision Making in the Face of Uncertainty

Clinicians are required to make decisions that balance risks and benefits for individual patients. Most commonly, there are fundamental uncertainties, particularly the risks for future untoward events that complicate decision making. Recent studies have raised questions about the risk of pneumonia among patients with chronic obstructive pulmonary disease (COPD) treated with inhaled corticosteroids, an agent commonly used to reduce exacerbations (1–3). Chen and colleagues (pp. 312) have now completed a retrospective study that will help clinicians with this problem (4).

An association of pneumonia with inhaled corticosteroid (ICS) use came to attention through clinical trials that compared ICS with placebo, primarily the Toward a Revolution in COPD Health (TORCH) study (4). An increase in “pneumonias” was noted in ICS-treated subjects compared with placebo-treated subjects. The nature of the “pneumonias,” however, remains unclear. Subject self-report was the most common criterion for recording an event. Supporting clinical information such as chest roentgenography, culture, or other supporting data was not systematically collected and, when pursued, was generally lacking (5, 6). Nevertheless, the observation of increased pneumonias for ICS versus placebo was consistently observed in many studies with several ICS medications and a pharmacoepidemiological study (1–3), although a retrospective combined analysis of several trials failed to show an increase with the ICS budesonide (6). Thus, while the nature of the events remains uncertain, it appears that study subjects (and their clinicians) are observing some kind of event that occurs among those treated with ICS.

A strength of randomized controlled prospective trials is that bias on enrollment is theoretically eliminated. On the other hand, differential drop out (for example, due to ineffectiveness of the placebo) can create bias for events that depend on the duration of exposure (7). In clinical trials of patients with COPD, there is consistently a higher dropout rate among placebo-treated subjects compared with those treated with ICS. Most of the reports of pneumonia associated with ICS in clinical trials adjusted for duration of treatment. However, this does not really account for severity of disease (i.e., those who dropped from a COPD study may be enriched for those who are at risk for pneumonia). Such an effect could create an artefactual increase in pneumonia among those treated with ICS.

Interestingly, exacerbations of COPD are consistently reduced with treatment with ICS, despite the increase in reports of pneumonia. This raises the question of definition of exacerbation and of pneumonia. Most commonly in clinical trials, an exacerbation is an event with an increase in symptoms of dyspnea, cough, and sputum that is sustained and more than usual day-to-day variation. The severity of the event is most commonly gauged by the need for increased treatment, including antibiotics (8). The same symptoms are cardinal features of pneumonia, which is also treated with antibiotics, and for this reason virtually all cases of self-reported pneumonia in a clinical trial may also be counted as exacerbations. Systemic symptoms including fever and fatigue are not differentiating features. Physical findings including rales, dullness, and bronchial breath sounds versus rhonchi, resonance, and bronch-vesicular breath sounds may be differentiating features, but are seldom well documented and

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