Non-eosinophilic asthma and the innate immune response

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Pathological heterogeneity of asthma

The concept that there may be heterogeneity of the underlying pathology of asthma has a long pedigree: 80 years ago, Rackemann suggested that a subgroup of patients with intrinsic asthma had disease driven by bacterial infection of the upper and lower respiratory tract and the authors of an early postmortem study were struck by the heterogeneity of lower airway inflammatory response in fatal asthma. However, since then the prevailing view, largely driven by bronchial biopsy studies of limited numbers of patients with relatively mild disease, has been that there are more similarities than differences in the pathology of subtypes of asthma. Thus, asthma is currently viewed as a disease driven by bacterial infection; chronic inflammation of structures embryologically linked to the airways, and inhaled stimuli such as hypertonic saline, endotoxin, ozone, cigarette smoke, other pollutants and occupational irritants. A common feature of these immune responses is the involvement of innate immunity, and Douwes et al have suggested that the interaction between elements of this primitive immune response and the airway might be important in the development of the airway hyper-responsiveness and variable air flow obstruction seen in non-eosinophilic asthma. Tumour necrosis factor (TNF) \( \alpha \) might be particularly important in this regard as treatment with the TNF\( \alpha \) antagonist etanercept has been shown to be associated with a significant improvement in airway responsiveness and air flow obstruction in patients with severe asthma.

The concept that activation of the innate immune response in the airway occurs in non-eosinophilic asthma has been investigated in a study reported by Simpson et al (see p 211) in this issue of Thorax. The investigators measured expression of innate immune response receptors and cytokines, the concentration of the proinflammatory cytokine IL8 and the levels of lipopolysaccharide and endotoxin in induced sputum in patients with asthma, bronchiectasis and controls. The group with asthma were subcategorised into inflammatory phenotypes based on the induced sputum differential inflammatory cell count; all were non-smokers. The authors found increased expression of mRNA for several innate immune response receptors and cytokines, increased IL8 and a trend to increased endotoxin concentration in induced sputum in patients who were classified as having neutrophilic asthma. Potentially pathogenic bacteria were identified in 43% of the patients with neutrophilic asthma, a finding that is in keeping with Rackemann’s identification of a subgroup with bacterial asthma. Overall, the inflammatory profile seen in neutrophilic asthma was similar to that seen in patients with bronchiectasis, although the sputum endotoxin concentration tended to be higher and the proportion with bacterial colonisation lower in patients with neutrophilic asthma. These findings strongly support the hypothesis that activation of the innate immune response occurs in non-eosinophilic asthma. The observations are cross-sectional, and it is important to investigate the effect of interventions such as bacterial eradication or removal of sources of inhaled endotoxin on the clinical and inflammatory expression of the disease before we can conclude that...
there is a direct link between these inflammatory mechanisms and airway dysfunction. The recent demonstration that treatment with telithromycin improves outcomes in patients with exacerbations of asthma provides some support for this view, but more studies on the role of infection in both stable and acute asthma are required before we can be sure.

One third of the patients with asthma studied by Simpson et al. had normal sputum neutrophil and eosinophil differential cell counts. The authors suggest the term paucigranulocytic asthma for this subgroup. Whether neutrophilic and paucigranulocytic asthma can be distinguished reliably and consistently, and to what extent sputum findings reflect stable differences in the underlying lower airway immunopathology or the cause of the pathology, remains to be determined. None of the inflammatory parameters assessed in induced sputum differed between normal controls and the patients with paucigranulocytic asthma, suggesting that airway hyper-responsiveness and variable air flow obstruction can occur independently of airway inflammation as measured by induced sputum. This finding, together with evidence that the patterns of lower airway inflammatory responses associated with other airway conditions such as cough and chronic obstructive pulmonary disease are heterogeneous, implies that it might be other factors such as the intrinsic characteristics of the airway or the site of the inflammatory response that determine the functional consequences. One key factor leading to airway hyper-responsiveness might be mast cell localisation within the airway smooth muscle as this has been observed in eosinophilic and non-eosinophilic asthma but not eosinophilic bronchitis.

A final point of interest is to speculate on the consequences of the coexistence of eosinophilic airway inflammatory responses with the more usual eosinophilic inflammatory response. An elegant series of studies on smoking and asthma shows quite clearly that this combination leads to a number of features associated with more severe airway disease including: more troublesome symptoms; more frequent exacerbations; a more neutrophil dominated lower airway inflammatory response; physiological evidence of involvement of the small airways; an accelerated decline in lung function; and evidence of airway and systemic corticosteroid resistance. Importantly, many of these features improve with smoking cessation. Could the effect of multiple inflammatory stimuli be an important and potentially modifiable factor leading to more severe airways disease? If so, then investigating the mechanisms of chronic neutrophilic airway inflammation, and the way it interacts with airway function and other airway inflammatory responses, has a wider importance.


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