

EDITORIAL

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Severe asthma: a consequence of over exuberant repair?

This editorial discusses the findings of the paper by Macedo et al. [4]

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There is an increasing recognition that asthma, especially severe asthma, is a complex condition [1]. It comprises of several dimensions in particular clinical expression of disease, disordered airway physiology and tissue injury and repair. The latter is manifest as airway inflammation and remodelling. Each dimension itself is complex with substantial heterogeneity. The clinical expression includes typical symptoms of breathlessness, wheeze and cough punctuated with episodes of disease worsening known as exacerbations. Individuals with asthma have varying degrees of each symptom and in some these occur in isolation. Similarly, variable airflow obstruction, airway hyperresponsiveness (AHR) and persistent airflow obstruction can be present to a greater or lesser extent between individuals. This heterogeneity also extends to inflammation and repair. With respect to inflammation over the last 20 years non-invasive assessment of asthma using sputum induction has led to the identification of new inflammatory phenotypes namely eosinophilic, neutrophilic and paucigranulocytic asthma [2]. Airway remodelling, which is a common feature of asthma occurs across severity and can be present even in childhood [3]. Understanding the interplay between these complex dimensions of disease is important as it will shed light on the pathogenesis of asthma and impact upon targeted therapy. Our need to define this heterogeneity is most important in severe disease as patients with severe disease present a clinically unmet need with the greatest morbidity and mortality.

In this issue of *Clinical & Experimental Allergy* Macedo et al. [4] have compared features of airway inflammation, remodelling and dysfunction in a group of severe asthmatics compared with those with moderate disease. As with previous studies, they found that there was tremendous variability in the intensity and pattern of inflammation and remodelling both within and between severity

groups [5, 6]. The pattern of inflammation in tissue and differential cell counts from sputum and bronchoalveolar lavage (BAL) did not differ between groups. However, they did identify marked differences in remodelling with increased airway smooth muscle mass and reticular basement membrane thickening in those patients with severe disease suggesting that severe asthma is a consequence of over exuberant repair. These changes in airway structure were associated with disordered airway physiology with a significant inverse correlation between post-bronchodilator forced expiratory volume in 1 s and AHR with sub-basement membrane thickening.

Increased airway smooth muscle mass is a consistent feature of asthma [5–7]. Benayoun et al. [5] in a comprehensive examination of airway remodelling across asthma severities with healthy controls and subjects with chronic obstructive pulmonary disease found that the strongest predictors of persistent airflow obstruction were sub-epithelial fibroblast number and airway smooth muscle hypertrophy. Similarly, Kaminska et al. [7] demonstrated that smooth muscle area was greater in biopsies from severe asthmatics with persistent airflow obstruction compared with those without. Taken together these studies suggest that ongoing remodelling particularly in severe disease contributes to the development of airflow obstruction. In contrast the relationship between airway remodelling and AHR is much more tenuous [6] with some reports suggesting that remodelling may protect against AHR [8].

Advances in the assessment of airway geometry by computerized tomography (CT) imaging have also confirmed that the airways in asthma, particularly in severe disease, are remodelled with qualitative [9] and quantitative [7, 10–12] evidence of bronchial wall thickening. On a par with airway remodelling the relationship between airway geometry and lung function is also complex with some studies reporting a strong association [10–12] whereas others have not [7]. Although these cross-sectional studies generally support a relationship between airway remodelling and dysfunction the natural history of this aspect of disease is unclear and longitudinal studies combining different modalities to assess

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remodelling together with measures of airway physiology are required.

Current asthma therapy does not exert effects upon airway smooth muscle mass and therefore whether these features improve together is unclear. Hence there remains the question of whether remodelling is central to the development of progressive disease or is an epiphenomenon. This dilemma may in part be addressed by the advent of bronchial thermoplasty [13]. This technique in animal models has demonstrated relative selective effects upon airway smooth muscle with reduction in airway smooth muscle mass, but re-epithelization of the bronchial mucosa. Studies in human disease have shown promise with improvements in symptoms and health status, but without improving airway physiology [13]. These studies have not included biopsies to measure the success of reducing airway smooth muscle mass and therefore have not yet been able to address the question of the relationship between remodelling, clinical expression of disease and airway dysfunction. Studies are ongoing to further understand the efficacy and mechanism of action of bronchial thermoplasty and are eagerly awaited.

Thickening of the reticular basement membrane has previously been reported to be increased in asthma [5–7, 14, 15]. Bourdin *et al.* [14] found this to be the most discriminate feature of severe vs. healthy controls with a sensitivity of 98% and specificity of 95%. However, reticular basement membrane thickening is also observed in non-asthmatic eosinophilic bronchitis [15], perhaps suggesting that reticular basement membrane thickening may reflect persistent active eosinophilic inflammation. In support of this view 10 weeks of treatment with anti-IL-5 monoclonal antibody therapy, which targets eosinophilic inflammation reduced reticular basement membrane thickening with concomitant reductions in expression of the matrix proteins laminin and tenascin [16]. A recent study of anti-IL-5 has extended these earlier observations to show that the wall area assessed by CT was reduced after 1 year treatment with anti-IL-5 compared with placebo [17]. This study did not comprehensively examine matched bronchial biopsies and therefore whether this attenuation of remodelling was mediated by effects upon sub-epithelial fibrosis or other features of airway remodelling is unknown. Importantly this study introduces the possibility that airway remodelling even in patients with severe refractory asthma may in part be reversed and that this can be measured using a non-invasive test.

In addition to airway smooth muscle mass and reticular basement membrane thickening, other components of remodelling need to be considered when interpreting the complexity of the relationship between structure and function such as matrix deposition, vascularity, and the role of fibroblasts, myofibroblasts and fibrocytes. For example, matrix deposition in the lamina propria and

within the airway smooth muscle bundle itself is altered in severe asthma in terms of its quantity and composition [18]. The mesenchymal progenitors, fibrocytes, are increased in number in the peripheral blood of severe asthmatics [19, 20]; are related to the degree of airflow obstruction [19] and are located within the airway smooth muscle bundle [20]. These fibrocytes may contribute to the increased airway smooth muscle mass. Not only the pattern of remodelling but also its site may be critical. It is likely that small airway inflammation and remodelling is a major contributor to airflow obstruction. However, this site is difficult to assess in terms of physiology and imaging and difficult to access by bronchoscopy. BAL provides some insight into the smaller airways and inflammation in this compartment may be related to AHR [4]. Therefore researchers need to be cognizant of the potential combinatorial effects of multiple aspects of remodelling at different levels within the airway tree in the development of airflow obstruction.

In addition to extending our understanding of the importance of airway remodelling in severe asthma, Macedo *et al.* [4] have confirmed the view that airway inflammation, particularly in the larger airway, can be dissociated with airway physiology. Eosinophilic airway inflammation and AHR can be dissociated as evidenced in non-asthmatic eosinophilic bronchitis [15] and AHR is unaffected by anti-IL-5 monoclonal antibody therapy in spite of marked reductions in eosinophilic inflammation [17]. However, importantly anti-IL-5 therapy has demonstrated efficacy in severe asthma with reduction in severe exacerbations [17]. This underscores that eosinophilic airway inflammation is a key risk factor in the development of asthma exacerbations, but also reconfirms that non-eosinophilic disease may be important. Studies in non-eosinophilic asthma suggest that factors acting through the innate immune pathways might play a role. Early trials of macrolide therapy are encouraging for non-eosinophilic asthma [21], but further studies of this approach and other therapies for this asthma phenotype are required.

Challenges for the future studies of remodelling in asthma include the need for longitudinal studies and the integration of complex clinical, genetic, physiological, imaging and pathological data. The use of non-invasive measures of airway inflammation and imaging will allow a more comprehensive assessment of the variability of disease and its natural history. The integration of these techniques with genome-wide association studies and potentially other 'omic' platforms using approaches such as systems biology are likely to present new phenotypes and targets. For this to be realized large networks of severe asthma specialists will need to work closely together using standardized assessments. Initiatives are underway to address this need and a more complete understanding of severe asthma is within our grasp.

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