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Inflammatory insights into airway remodelling in asthma

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Treatments for severe asthma have taken great strides recently with targeted therapies against immunoglobulin E and interleukin-5, alongside others well into phase three studies. Perhaps because of these advances there appears a groundswell of opinion that the disease is ‘fixed’, which is wrong; approximately 10% of the Western population suffer from asthma, whilst its prevalence and mortality grow, resulting in a substantial individual and societal burden.[1] Clinically, asthma is characterized by symptoms due to a combination of airway inflammation and airway hyper-responsiveness leading to bronchoconstriction. Asthmatic airway inflammation is most commonly eosinophilic, though in some patients neutrophils are predominant, each of these (and a combination of both) can be termed granulocytic inflammation. A minority of patients have no apparent airway inflammation, then classified paucigranulocytic. Structurally, asthmatic airways undergo changes collectively termed ‘airway remodelling’, demonstrating increased mucus-secreting goblet cells in the epithelium, thickening of the sub-epithelial collagen layer, as well as increases in airway blood vessel number, airway smooth muscle mass and muscle volume. Although it has been difficult to directly confirm, the current consensus (some might say dogma)[2] is that airway remodelling contributes to the observed decline in lung function and development of fixed airway obstruction seen in some chronic asthmatics.

In concert with the uncertainty around its significance, the cause(s) of airway remodelling are unknown, though airway inflammation has long been considered the culprit. Against this, remodelled airways are detectable in wheezy children prior to a formal diagnosis of asthma where both airway inflammation and airway remodelling are present simultaneously.[3] If airway remodelling is not being driven by inflammation, then what could be the cause? Application of mechanical force to epithelial cells and lung slices in vitro, mimicking the compressive mechanical environment of constricted airways,[4] induces goblet cell hyperplasia, collagen production from fibroblasts, the production of mediators promoting airway smooth muscle contraction and, most recently reported in our laboratory, contractility and proliferation of airway smooth muscle.[5–9] Some of these findings have been directly confirmed in human studies, suggesting that remodelling may be induced by deformation of the airway epithelium in the absence of additional airway inflammation.[10]

Despite these data, it is still unclear if airway remodelling in asthma is solely driven by inflammation (appears unlikely), solely driven by mechanical forces (equally unlikely) or if there are aspects of the remodelling process that are more or less influenced by each of these, or as yet unidentified stimuli. In a recent publication in *Respirology*, Elliot *et al.* demonstrate that specific features of airway remodelling may be distinguished as associated with airway inflammation or not associated with airway inflammation in asthma.[11] Their work implies that both airway inflammation and other stimuli can induce airway remodelling, and that specific aspects of remodelling may be distinguished by the predominant roles those stimuli play during its development.

Using post-mortem tissue from control subjects, fatal cases of asthma and non-fatal cases of asthma where patients died with, rather than of their respiratory disease, the authors retrospectively determined the relationship between granulocytic airway inflammation and airway remodelling. Inflammation was evaluated by counting eosinophils and neutrophils in airway sections, whilst remodelling was assessed using multiple parameters including measures of airway wall area, reticular basement membrane thickness, luminal mucus, smooth muscle volume and thickness and the density of extracellular matrix within the muscle layer. Features of airway remodelling were found to be differently associated with paucigranulocytic and granulocytic asthma. In paucigranulocytic asthma, remodelling included increased thickness of the airway smooth muscle and the reticular basement membrane layers, whereas in granulocytic asthma an additional increase in airway wall thickness and increased airway narrowing due to airway smooth muscle shortening and mucus obstruction were seen. The authors concluded therefore that some features of remodelling are inflammation dependent, whilst others are not.

The main question raised by this analysis is that of causation; the coexistence of markers of airway remodelling with inflammation does not imply that inflammation induced those changes, though of course that is possible. This is especially important in a retrospective study with incomplete clinical information, including duration and severity of disease, medication use and environmental exposure to antigen or tobacco smoke—variables that may coexist and influence both inflammation and remodelling. The report does not investigate the possibility that airway inflammation is a necessary but not sufficient stimulus to induce airway remodelling; measures of disease control, including frequency of exacerbations and symptom scores, could address some of this but were not available. Additionally, the stability of airway inflammatory phenotypes in asthma, especially fatal asthma is currently unknown; adding another layer of complexity when interpreting this necessarily single time-point study.

Editorial

Importantly, this study suggests that airway remodelling, rather than being a single entity, may be usefully subdivided into its component parts, each with potentially different driving pathways. As inflammation appears associated with some but not other aspects of the remodelling process, this implies that different stimuli are driving some but not other features of remodelling. This tallies with clinical experience; some patients develop a mucus hypersecretory phenotype, whilst others demonstrate a rapid decline in lung function and

fixed airways disease. Data from the current study encourage us to not only endeavour to better understand the apparent dissociation between inflammation and remodelling, but also better understand the specific and different pathways involved, to develop targeted therapies towards specific elements of the airway remodelling seen in asthma, a disease which is certainly not yet ‘fixed’.

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