

EDITORIAL

Airway remodelling in asthma: It's not going away

Key words: airway remodelling, asthma, chronic obstructive pulmonary disease, high-resolution computed tomography.

Airway remodelling can be defined as a change in the structure of the airway wall, which may involve any or all parts of the wall. It is well recognized from morphometry studies of post-mortem lungs, where airway wall thickening is greater in severe, fatal asthma compared with stable asthma, particularly ASM thickness.¹ Airway remodelling is often inferred through measurements of wall thickness by high-resolution computed tomography (HRCT). The large body of published evidence using HRCT clearly and consistently shows increased wall thickness in asthmatic compared with non-asthmatic individuals. Yet, how certain are we that changes in wall thickness measured by HRCT truly reflect airway remodelling, and furthermore, that a therapy driven reduction in wall thickness is evidence for reversal of airway remodelling?

The study of Hoshino *et al.*² in this edition of the Journal is a case in point of why it is necessary to carefully interpret measurements of airway wall thickness derived by HRCT. In the study, the relationship between HRCT measured airway wall thickness and periostin was investigated in corticosteroid naïve asthmatic subjects. Periostin is a protein expressed in epithelial and matrix cells that is up-regulated by TH2 cytokines IL-4 and IL-13 and is implicated in basement membrane fibrosis. It therefore has the potential to be a marker of TH2 inflammation mediated airway wall remodelling. The authors reported that serum periostin correlated with airway wall thickness and both decreased with inhaled corticosteroid treatment in parallel with a fall in sputum eosinophils. The study very nicely demonstrates the utility of periostin as a marker of TH2 inflammation and disease severity.

Disclosure Statement: Between 2011 and 2015, GKG has received various travel sponsorships from Boehringer Ingelheim, Novartis Pfizer, AstraZeneca and GlaxoSmithKline for travel and accommodation to attend local, national and international, meetings that include Pharmaceutical Industry sponsored meetings and Scientific Society meetings. GKG's research work is conducted at the Woolcock Institute of Medical Research, which is partly supported by research and unrestricted grants, and consultancy fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini, MundiPharma and Novartis. GKG provides consultancy services related to asthma and COPD, which include services to advisory boards and delivering lectures at local, national and international meetings. GKG's research group is supported from competitive grants arising from local philanthropic foundations, Sydney University, The National Health & Medical Research Council of Australia and The Australian Lung Foundation.

Without further qualification, the above findings also suggest that inflammation (eosinophilic) drives airway remodelling and treatment with inhaled corticosteroids reverses the remodelling process. This paradigm sounds sensible in light of the circumstantial evidence. Uncontrolled eosinophilic inflammation is associated with increased decline in FEV1, independently of age of onset of disease. Conversely, earlier treatment in newly diagnosed asthma with inhaled corticosteroids, which are highly effective against eosinophilic inflammation, is associated with reduced loss of FEV1 compared with delaying the start of inhaled corticosteroids over a 2 year period.³

A more cautious consideration of the same HRCT data, in view of imaging limitations, draws quite different conclusions. Interpretation of changes in airway wall thickness on HRCT is not straightforward because changes in thickness could be due to reduction in any component of the airway wall including oedema, blood vessels, cells, matrix or even mucus. Given the subjects were steroid naïve and treated for 4 months, much of the changes in wall thickness could well be due to reduced eosinophilic inflammation alone without any effects on remodelling. Notably, basement membrane decreases in thickness after 3-9 months of treatment, while inflammation decreases within 3 months.⁴ Put simply, treating patients with an anti-inflammatory drug reduces inflammation, but whether it reduces airway remodelling within the same time period remains to be seen.

The results of Hoshino *et al.* raise questions beyond the biomarker potential of periostin. That is, it can be questioned whether airway wall remodelling can be therapeutically targeted and whether inflammation can cause remodelling. The late Ann Woolcock often asked 'why don't all atopic subjects get asthma?' a question as relevant today as it was 15 years ago. Airway inflammation relates poorly to bronchial biopsy measures of airway remodelling. The presence of neutrophilic and pauci-granulocytic inflammation particularly in elderly subjects with asthma and in late onset asthma raises the question of whether inflammation of any kind, not just TH2 high, can drive or modify airway remodelling. Control of inflammation with corticosteroids is not very effective in controlling remodelling, either in preventing lung function decline or reversing the microstructure.⁵

The drivers of airway remodelling other than the inflammatory cells need to be considered. Epithelial cells, dendritic cells and tissue macrophages are 'on the front line' in relation to handling inhaled particles. Therefore, these cells are potentially important in driving changes in airway structure⁶ given the signalling between those cells and fibroblasts, airway

smooth muscle and inflammatory cells. The extracellular matrix may also play a role in airway remodelling. The matrix cleavage products are pro-inflammatory and pro-proliferative so that direct proteolytic effects of inhaled particles, such as house dust mite DerP1 protein, by degrading matrix proteins could initiate and perpetuate the remodelling process. In this situation, remodelling would primarily be initiated by a direct toxic inhalant effect with inflammation being a secondary but important modifying phenomenon. In addition, there is both *in vitro* and *in vivo* evidence that mechanical stress applied to airways by bronchoconstriction may alter structure.⁷

An alternate and intriguing possibility is that the structural alterations in asthma are there from the very beginning. Infants who exhibit airflow limitation at birth are more likely to develop asthma later in life.⁸ Even before asthma is diagnosed in children, airway smooth muscle is increased⁹ and basement membrane is thickened,¹⁰ albeit findings are inconsistent. Airway smooth muscle thickness relates to disease severity but not to either duration or age of onset of disease.¹ Taken together, these observations further argue against inflammation being the mechanistic origin for histologically characterized remodelling, and are instead consistent with the possibility that airway remodelling was present from the earliest course of the disease. Airway remodelling in asthma may not be going away!

If we better understood the origin of remodelling, then treatments beyond inhaled corticosteroids can be trialled. We as clinicians and researchers desperately need a simple and non-invasive marker of airway remodelling, and to this end, well conducted studies like that of Hoshino *et al.* are informative. A marker of remodelling would be clinically useful if it could predict decline in FEV1 and if its change predicts treatment success in altering FEV1 trajectory. Although such longitudinal studies might seem tedious, they are nevertheless being undertaken in chronic obstructive pulmonary disease and this surely must flow into asthma research. What is clear is that HRCT is not sufficient to adequately resolve these issues and imaging techniques that can differentiate the different layers of the airway wall, such as optical coherence tomography,¹¹ need to be further developed for research into airway remodelling.

Acknowledgements

The authors acknowledge receipt of funding from the NHMRC Centre for Research Excellence in Severe Asthma (#1078579—

GGK), NHMRC Project Grants #1031701 (GGK), #1063068 (GGK, PBN), #1027218 (PBN) and NHMRC Career Development Fellowship #1045824 (PBN)

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