Airway wall remodelling in asthma

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Although reversibility of airflow obstruction has traditionally formed part of the definition of asthma, it is apparent that airflow obstruction in asthma is often not completely reversible. A number of investigators have reported that asthmatic patients frequently have persistent lung function abnormalities despite clinical remission. In one study an attempt was made to maximise lung function by means of bronchodilators and, if necessary, oral corticosteroids in a large group of patients with chronic asthma. Many subjects were nevertheless found to have a degree of irreversible airflow obstruction, irrespective of whether or not they had smoked, and the degree of impairment of lung function correlated with both the duration and severity of the disease. Community studies performed over periods of six years and 18 years in rural communities in America and Western Australia, respectively, have established that the rate of decline of lung function is greater in asthmatic patients than in non-asthmatic patients. In one of these studies, for example, the average change in forced expiratory volume in one second (FEV1) per year for adult men with asthma was 24 ml compared with 6.3 ml for non-asthmatic men. The rate of decline in FEV1, appears to be most pronounced in those patients with the greatest degrees of airflow obstruction, the so-called “horse-racing” effect.

Taken together these studies indicate that asthma alone is capable of leading to irreversible airflow obstruction. An important factor in this process is believed to be the development of structural changes (remodelling) in the airway wall. The first indications that such changes are a feature of asthma came from post-mortem examinations. In a pioneering study in 1922 Huber and Koessler reviewed the necropsy findings of 21 patients who had died from severe asthma. In addition to partial or total occlusion of the bronchial lumen by mucous plugs and extensive cellular infiltration of the bronchial wall, they reported that a prominent feature in many of the cases examined was the presence of thickening of the airway wall. Detailed measurements of airway wall dimensions were performed in six of these subjects and the results were compared with those from a group of seven non-asthmatic subjects who had died from other causes. In bronchi of external diameter greater than 2 mm the thickness of the subepithelial layer, the thickness of the muscle layer, and the total wall thickness were all found to be increased in those with asthma.

The use of morphometric techniques to define structural changes in the airway wall has since been greatly extended. Important preliminary observations were made using porcine, guinea pig, and human airways. These studies revealed that the internal perimeter and wall area remain relatively constant despite changes in smooth muscle length and lung volume whereas other parameters, such as external perimeter and luminal area, vary markedly. Many of the problems encountered when comparing airways from different sites and from different subjects can therefore be overcome by the use of internal perimeter as a marker of airway size. This approach was first used to quantify airway dimensions in fatal asthma. In a study of post-mortem specimens from 18 asthmatic and 23 non-asthmatic subjects the wall area was found to be significantly increased in the airways of those with asthma. When membranous airways of internal perimeter <2 mm and ≥2 mm and cartilaginous airways of <10 mm and ≥10 mm were considered separately, the increase in wall area was found to involve all airway groups. Comparable changes have also been described in resected and post-mortem lung specimens from subjects with non-fatal asthma, although in these cases the differences appeared to involve predominantly the membranous and small cartilaginous airways.

The contribution of individual components of the airway wall to the total increase in wall area has been analysed. A number of studies have reported that the area of airway smooth muscle is substantially increased in both large and small airways in cases of fatal asthma. Detailed morphometric studies have suggested the existence of two distinct patterns of smooth muscle thickening – those cases where this process is confined to the central airways and those where the changes involve the entire bronchial tree. It was originally believed that the predominant pathology of the smooth muscle of the airway was that of cellular hyperplasia rather than hypertrophy, as the number of smooth muscle nuclei was reported to be increased approximately threefold. However, a more recent study using accurate three-dimensional reconstruction has suggested that, although the increase in airway smooth muscle results from hyperplasia when this process is confined to large airways, hypertrophy predominates when the smaller airways are also involved. Several investigators have reported that the proportions of bronchial wall area occupied by mucous glands are also increased in fatal asthma, although airway size was not precisely standardised in these early studies. In addition, the epithelium, submucosa, vascular compartment, and adventitia all have been shown to contribute to the total increase in wall area.

Other evidence for the presence of structural abnormalities in the airway wall in patients with asthma derives from radiological studies. Bronchial wall thickening is frequently evident on plain radiographs and more detailed information is provided by high resolution computed tomographic (CT) scanning of the lungs. In surveys of patients with asthma of varying severity and aetiology, CT evidence of bronchial wall thickening has been reported in up to 90% of cases. The presence of abnormalities on the CT scan is related to both the duration and clinical severity of the disease. In another study high resolution CT scanning was used to quantify the thickness of the bronchial wall at the level of the intermediate bronchus in asthmatic subjects, with and without fixed airflow obstruction, as well as in non-asthmatic control subjects. No difference was detected between the three groups in bronchial wall thickness, expressed in relation to outer diameter, which may reflect the relative insensitivity of CT scanning as a means of quantification. However, in the subjects with fixed airflow obstruction there was a direct correlation between bronchial wall thickness and airway reactivity.

Altered airway structure in asthma may result in altered airflow function in a number of ways. An increase in the amount of airway smooth muscle will allow greater shortening in response to a bronchoconstrictor stimulus, and an increase in the adventitial area may lead to un-
coupling of the distending forces of parenchymal recoil from the forces tending to narrow the airways.\textsuperscript{20} In the morphometric studies described above the degree of smooth muscle shortening required to occlude the lumen was calculated to be lower in the asthmatic airways.\textsuperscript{14} This analysis has been extended using a computer model developed to assess the effects of airway wall thickening and airway smooth muscle shortening on airway resistance.\textsuperscript{30} Using the measurements obtained from post-mortem specimens this model suggests that baseline resistance may be only slightly increased if the airway wall thickens without encroaching on the lumen, but when the smooth muscle shortens even by modest amounts the increase in wall thickness will have an exaggerated effect on the airway lumen and markedly increase airway resistance.\textsuperscript{35} The model also predicts that changes in the smaller conducting airways, which have smooth muscle that completely encircles the airway lumen, will have a much greater effect than similar changes in the more central airways.\textsuperscript{36} Thus, the magnitude of airway wall thickening that is observed in the airways of subjects with asthma may contribute substantially to airway hyperresponsiveness in addition to airflow obstruction.

Tissue remodelling in asthma has received particular attention in relation to one specific component of the airway wall – namely, the specialised region of extracellular matrix beneath the bronchial epithelium. Abnormalities in the basement membrane zone in asthma were first recognised in many early post-mortem studies.\textsuperscript{10,32–35} These reports described broadening and hyalinisation of this region, appearances frequently described as basement membrane thickening, with appropriate histological stains suggesting that these changes resulted largely from collagen deposition. Rigid bronchoscopy has provided evidence that similar changes are also present in asthmatic subjects\textsuperscript{24,36} and subsequently these observations have been confirmed in many studies using fibroptic bronchoscopy to obtain bronchial biopsy specimens from subjects with mild asthma.\textsuperscript{37–39} The use of electron microscopy to examine the ultrastructure of the basement membrane in asthma has indicated that the organisation of the lamina rara and lamina densa is well preserved but that the lamina reticularis is greatly increased in depth, corresponding to the apparent “basement membrane thickening” described in light microscopic studies.\textsuperscript{112} Immunohistochemical analysis has suggested that this thickened layer is largely composed of collagen types III, V and, to a lesser extent, I and fibronectin.\textsuperscript{29} However, consistent with the electron microscopic findings, the distribution of laminin and collagen IV was reported to be unaltered in asthma.\textsuperscript{39}

The appreciation that the principal components of the thickened layer are interstitial collagens suggested that the overlying bronchial epithelial cells are not responsible for its deposition and prompted a search for an appropriate mesenchymal cell population. Using an antibody raised against pericrytal fibroblasts in the gastrointestinal tract, a specialised network of fibroblastic cells with long cytoplasmic extensions was identified beneath the lamina reticularis.\textsuperscript{43} Ultrastructural analysis demonstrated the presence of abundant polyribosomes and occasional parallel arrays of thin filaments consistent with contractile apparatus, indicating that these cells are myofibroblasts.\textsuperscript{44} Although present in normal subjects, the numbers of subepithelial myofibroblasts are increased in asthma and these numbers correlate with the degree of collagen thickness, suggesting that these cells are indeed responsible for the deposition of this layer.\textsuperscript{39}

The significance of subepithelial fibrosis in asthma is uncertain. No correlation has been demonstrated between the thickness of this layer, measured in large bronchi, and clinical or physiological indicators of asthma severity.\textsuperscript{39} The myofibroblast numbers do, however, correlate with the duration of asthma\textsuperscript{45} and, in this respect, support the findings of Brown et al\textsuperscript{46} in their analysis of irreversible airflow obstruction and duration of asthma. The myofibroblast and collagen findings in large airways may act as a marker for remodelling more generally in the airways, particularly in the small airways which represent the predominant site of airflow obstruction in obstructive lung disease.\textsuperscript{44}

An important goal of current asthma research is to understand the dysfunction in regulatory mechanisms responsible for remodelling of the airway wall. Many growth factors and other mediators have the potential to be implicated in this process on the basis of their in vitro biological properties. These include transforming growth factor-\(\beta\),\textsuperscript{47} platelet-derived growth factor,\textsuperscript{48} basic fibroblast growth factor,\textsuperscript{49} cytokines such as tumour necrosis factor-\(\alpha\) and interleukin 4,\textsuperscript{50} the peptide mediator endothelin,\textsuperscript{51} and miscellaneous additional molecules including histamine\textsuperscript{52} and trypsin.\textsuperscript{53} All of these factors are able either to elicit a mitogenic response in fibroblasts and/or airway smooth muscle cells or to promote connective tissue synthesis by these cells. In several cases increased expression of these mediators has been identified in the airways in asthma.\textsuperscript{53–57} However, functional studies will certainly be required before any conclusion can be reached regarding the in vivo importance of an individual mediator.

The clinical relevance of airway wall remodelling in asthma is highlighted by a report from Finland by Hahtela et al\textsuperscript{58} in a comparative longitudinal study of a topical inhaled corticosteroid (budesonide) and a short acting \(\beta_2\) agonist (terbutaline) they found that the potential to reverse airway obstruction and measures of bronchial responsiveness was impaired in patients in whom anti-inflammatory therapy was delayed. It is thus possible that these structural changes are more difficult to reverse, once they have occurred, than they are to prevent with prophylactic therapy. The ability of structural changes to develop early in the disease is illustrated by their occurrence in young children\textsuperscript{42} and in occupational asthma following a relatively brief period of exposure to the sensitising agent,\textsuperscript{23} and is also suggested by a report that the greatest loss of lung function in asthma occurs in the early years following diagnosis.\textsuperscript{59} Further studies addressing the effect of treatment on the reversibility and prevention of these structural changes are required as, although inhaled corticosteroids reduce symptoms, improve lung function, modify bronchial hyperresponsiveness, and reduce eosinophilic airway inflammation in asthma, there is only one study suggesting that this mode of treatment is able to reverse airway collagen deposition\textsuperscript{61} with several others reporting no effect.\textsuperscript{52,65} Should these studies confirm the relative lack of reversibility of established fibrosis, then this would reinforce the argument for the early introduction of prophylactic medication in patients with mild asthma.

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growth factors and their receptors


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