

Fibrosis and airway remodelling

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Summary

The term 'airway remodelling' is now widely used to refer to the development of specific structural changes in the airway wall in asthma. Particular interest has focused on subepithelial fibrosis, myofibroblast accumulation, airway smooth muscle hyperplasia and hypertrophy, mucous gland and goblet cell hyperplasia, and epithelial disruption. The presence of these features is generally accepted, but further studies are still required to define the changes occurring more precisely at the pathological and ultrastructural levels. Attention also needs to be directed towards the existence of such changes in small airways. The natural history of the response has not been well described: remodelling is present in the airways of asthmatic children and of adults with newly diagnosed asthma, and studies that have attempted to relate the extent of remodelling to disease severity have produced conflicting findings. The role of remodelling in the progressive decline in lung function leading to fixed airflow obstruction seen in some patients is also unclear. Epidemiological studies are currently hindered by the absence of a useful non-invasive marker of remodelling. Airway remodelling is frequently assumed to be a consequence of chronic inflammation, but the precise relation between the remodelling and inflammatory components in asthma is unclear. The cellular and molecular events underlying the remodelling process are also poorly understood. There is therefore a need for the development and characterization of animal models that will allow these issues to be explored. Finally, the ability of currently available anti-asthma therapies to prevent or reverse airway remodelling is uncertain. There is some evidence that early treatment with inhaled corticosteroids can lead to improved outcome in asthma but this needs confirmation. Studies addressing the ability of corticosteroid treatment to reverse established structural changes have not produced consistent findings, and there is little information with regard to other therapies such as theophylline and antileukotriene agents. Effective treatment of airway remodelling may require the development of novel therapies directed against appropriate targets.

Keywords: airway remodelling, asthma, inflammation, early intervention, fibrosis, therapy, corticosteroids

Introduction

The principal features of airway remodelling in asthma are: subepithelial fibrosis, myofibroblast hyperplasia, airway smooth muscle hypertrophy/hyperplasia, mucous gland and goblet cell hyperplasia, and epithelial disruption. In addition, a recent report has suggested that perhaps perichondrial fibrosis should be added to this list [1]. With regard to the fibrotic response, the myofibroblast may be a

key cell. In an animal model of bleomycin-induced pulmonary fibrosis it was myofibroblasts rather than fibroblasts that were responsible for the excess matrix deposition [2]. The excess matrix deposition that is a prominent feature of asthma is typically composed of collagen I, collagen III and tenascin [3–5]. In addition, there may be increased expression of collagen V and fibronectin.

These descriptive studies need to be paralleled by functional studies to understand their importance. For example, how do these alterations in the matrix affect the chemotaxis or other functions of inflammatory cells? Moreover, most of this information comes from bronchoscopy-based studies,

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which sample the large airways. Attention is now shifting towards the role of the small airways in asthma as these appear to be the predominant site of airflow obstruction. There is evidence from post-mortem morphometric studies that the increase in wall area observed in large airways occurs equally in the small airways [6]. We need to direct our attention towards *in vivo* studies of remodelling in the small airways, perhaps using the technique of transbronchial lung biopsy, as has been used to address the role of inflammation [7]. This is particularly important now that we have therapies that are able to target the smaller airways [8].

Natural history of airway remodelling

There is a lack of knowledge regarding the natural history of the remodelling response. It is clear that mucosal inflammation is present even in newly diagnosed asthma [9], and it seems likely that remodelling will also be present. However, it is not known how long before diagnosis that remodelling occurs. Studies in occupational asthma have suggested that only a relatively short period of exposure to an occupational sensitizer is required for remodelling to occur [10].

Several studies have attempted to correlate the degree of remodelling and the severity of asthma, but conflicting information has been obtained. Chetta *et al.* [11] measured the depth of subepithelial collagen deposition and found that, in comparison with control subjects, there was a stepwise increase in the depth of this layer in asthmatics with mild, moderate and severe disease (Fig. 1). In a related publication, these authors also reported correlations between the thickness of the subepithelial layer and physiological indices such as FEV₁ and PC₂₀ in a large group of asthmatics [12]. Minshall *et al.* [13] used a semiquantitative grading system to score the degree of fibrosis, not just in the subepithelial region but throughout the airway wall, and were able to show

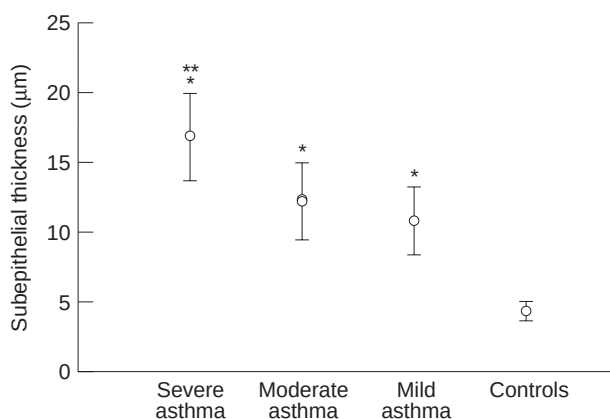


Fig. 1. Subepithelial layer thickness and disease severity. Redrawn with permission of the American College of Chest Physicians from [11].

a progressive increase in fibrosis with increasing severity of asthma. In contrast, Chu *et al.* [14] in a study of similar design, found no significant difference in collagen deposition (total collagen or collagens I and III) between control subjects and patients with differing degrees of asthma severity. Thus, the relationship between airway remodelling, at least as assessed in this way, and disease severity is unclear at present.

The role of airway remodelling in the progressive decline in lung function and its relationship to the development of irreversible airflow obstruction is unclear. It is often assumed that remodelling is an important factor. However, high-resolution computed tomography (CT) scanning demonstrates a number of abnormalities in asthmatic airways including bronchiectasis, emphysema and linear atelectasis, that may also play a role [15]. Finally, the resolution of the remodelling response is an area where there is little information. For example, it is unclear what happens in children who grow out of their asthma. In occupational asthma, withdrawal of exposure from the sensitizing agent will result in some regression of remodelling [16].

Inflammation and remodelling

The precise relationship between remodelling and inflammation is unclear. It is often assumed that there is a linear progression between an initiating stimulus leading to inflammation, which in turn leads to remodelling. Alternatively, however, the same stimulus could independently lead both to inflammation and to remodelling (Fig. 2). The cellular and molecular events underlying the remodelling process are also poorly understood. There is therefore a need for the development and characterization of animal models that will allow these issues to be explored.

Airway remodelling as a target for therapy

The ability of currently available anti-asthma therapies to prevent or reverse airway remodelling is uncertain. Several

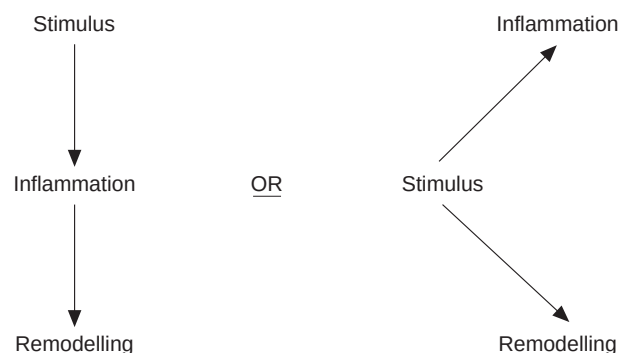


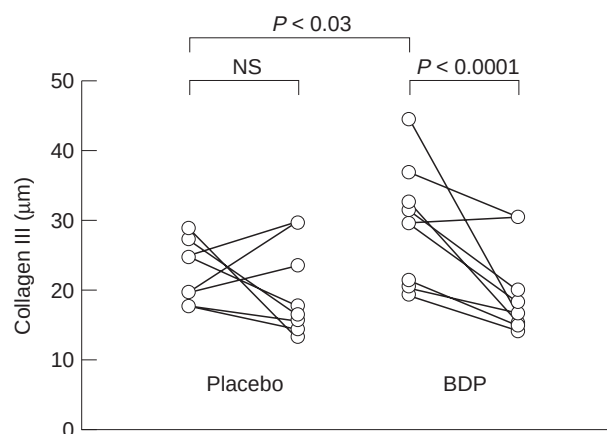
Fig. 2. Remodelling and inflammation.

Table 1. Basement membrane reticular collagen thickness in control subjects and before and after corticosteroid treatment in asthmatics [20]

Control subjects	8.2 ± 0.5 µm
Asthmatics	
Pre-budesonide	11.0 ± 0.6 µm
Post-budesonide	10.8 ± 1.0 µm
Long-term steroids (> 6 months)	11.0 ± 0.7 µm

epidemiological studies have suggested that early intervention may improve the long-term outcome in asthma [17–19], but these studies have concentrated on outcome measures such as lung function. None of these studies has directly related this to the remodelling process.

Short-term studies addressing the ability of existing treatments to reverse airway remodelling have mostly been carried out using corticosteroids and there is conflicting data. In an early study, Jeffery *et al.* [20] used electron microscopy of airway mucosal biopsies to measure the depth of subepithelial collagen deposition in control subjects and in patients with asthma before and after budesonide treatment. In asthmatics at baseline (prebudesonide), there was a significant increase in the thickness of basement membrane reticular collagen compared with control subjects, although this increase was fairly modest (Table 1). Following 4 weeks of treatment with low-dose budesonide there was no significant change in the depth of this layer. Furthermore, in a group of asthmatics on long-term steroids (average 3.7 years), subepithelial collagen layer (Table 1) measurements were similar. Other investigators have come to different conclusions. Trigg *et al.* [21] used immunocytochemistry to measure collagen III in the airway basement membrane and found that after a 4-month treatment period with high-dose beclomethasone dipropionate (BDP), there was a significant reduction in the depth of collagen III deposition as compared with the placebo-treated group (Fig. 3). However, despite randomization, the two groups were not well matched for baseline collagen deposition. Similarly, a significant decrease in basement membrane thickness following fluticasone propionate treatment but not placebo treatment was reported by Olivieri *et al.* [22]. Since neither of these two studies included a control group of healthy subjects, it is not known whether the degree of regression that was achieved was towards normal values. There is little information with regards to the effects of other therapeutic modalities on remodelling. *In vitro* studies suggest that both antileukotrienes and theophyllines may have relevant effects on fibroblast proliferation, but there is no information from *in vivo* studies.

**Fig. 3.** Corticosteroids and airways remodelling. Redrawn with permission of the American Thoracic Society from ref [21].

Novel treatments

Effective treatment of airway remodelling may require the development of novel therapies directed against appropriate targets. Numerous candidate mediators have been proposed as being implicated in the remodelling response as listed in Table 2. Almost every mediator is overexpressed in the airway wall in asthma and it is not known which are the key mediators. We need to select appropriate targets and assess the overall *in vivo* response. Animal models such as the McMaster model, in which adenoviruses are used to over-express specific cytokines *in vivo* in rat lung, have provided some information. In this model, tumour necrosis factor (TNF) [23] and GM-CSF [24] induce predominantly an inflammatory response with some evidence of fibrosis, whereas transforming growth factor-beta (TGFβ) induces a dramatic fibrotic response with some inflammation [25]. Measurement of cytokines has indicated that TGFβ may be acting downstream of both GM-CSF and TNF. Therefore, TNF and GM-CSF may be interesting as targets for inflammation in asthma but not as targets for remodelling.

Finally, efforts should be directed towards identifying a non-invasive marker of airway remodelling. Induced sputum

Table 2. 'Fibrogenic' mediators

Peptides	ET-1, ET-3
Cytokines	IL-1, IL-4, IL-11, IL-13, TNFα, GM-CSF
Growth factors	TGFβ, PDGF, bFGF, IGF, CTGF
Others	Histamine, tryptase, thrombin

ET, endothelin; IL, interleukin; GM-CSF, granulocyte macrophage colony-stimulating factor; TGF, transforming growth factor; PDGF, platelet derived growth factor; bFGF, basal fibroblast growth factor; IGF, insulin-like growth factor; CTGF, connective tissue growth factor.

perhaps provides the most promising way forward and it would be worth exploring matrix components and matrix degradation products, cytokines, growth factors, and matrix metalloproteases (MMPs) and TIMPS. Novel forms of imaging could also be useful. High resolution CT has been used by a number of groups and provided some information [15] but it lacks sensitivity and there are concerns about the radiation dose following repeated use in relatively healthy subjects. Optical coherence tomography, which has been used in the context of sleep-disordered breathing to detail upper airway anatomy [26], might provide some useful information on airways remodelling.

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