Airway Remodelling

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Asthma is a chronic inflammatory disorder of the airways, often associated with atopy and characterized by variable airflow limitation and airway hyperresponsiveness to various stimuli[1]. Airway inflammation, a central feature of asthma which has been widely demonstrated in patients with chronic asthma, is correlated to clinical severity of the disease[2,3]. Although it is a quite new concept, it may prove to be essential for understanding of the development of persistent asthma with chronic abnormal lung function. Recently, the term "airway remodelling" has been applied to structural changes seen in asthmatic airways. The legacy of ongoing inflammation is a pattern of nonacute changes leading to thickening of the airway wall[4], including smooth muscle hypertrophy / hyperplasia[5], subepithelial and submucosal collagen deposition[6,7], and increased vascularity[8]. These components of remodelling have an undetermined effect on symptom control, lung function, airway reactivity and outcome from acute attacks of asthma. The basement membranes, thin layers of specialized extracellular matrix, are not only supporting structures for epithelial cell growth but also actively participate in cellular interactions[9,10]. Accumulation of fibrous proteins like collagens, elastin, tenascin, fibronectin and laminin change the function and structure of the basement membrane[10,11,12]. Fundamentally, thickening of the basement membrane may be a protective mechanism preventing inflammatory cells and proteins, which leak from the dilated submucosal vessels, to intrude the epithelium and damage its integrity.

Eosinophils and mast cells are essential modulators of lung remodelling. The asthmatic airway is characterized by eosinophil infiltration and activation with evidence of degranulation. There are numerous factors that contribute to eosinophil recruitment to the airways, including cytokines (i.e., IL-3, IL-5, and GM-CSF), chemokines (eotaxin and RANTES), and adhesion molecules (ICAM-1 and VCAM-1)[13]. Eosinophils play an important role in remodelling by producing metalloproteinases, collagenase, and growth factors (i.e. TGF-b and PDGF), which regulate the proliferation and matrix production of fibroblats and other stromal tissues[14].

Mast cell hyperplasia is a characteristic feature of the asthmatic airway and is a frequent finding in the tissue fibrotic and remodelling responses[15]. Both in vivo and in vitro studies show that mast cells and their mediators can play an important role in chronic inflammatory and remodelling disorders[13]. A major product of mast cell is tryptase, a serine protease that is stored preformed in the mast

cell granule[16]. Human tryptase is a potent mitogen for epithelial cells[17], fibroblast[16], and bronchial smooth muscle cells[18]. It stimulates collagen secretion from fibroblasts[16] and IL-8 relase from epithelial and endothelial cells, as well as up-regulating cellular expression of ICAM-1[17,19].

Animal models are useful for elucidating the pathological changes and underlying mechanisms involved in asthma. Blyth and co-workers[20] developed a murine model of allergen-induced airway inflammation and epithelial phenotype change, at the time course of these events. They used ovalbumin sensitized BALB/c mice and challenged them by multiple intratracheal instillations of ovalbumin by non-surgical technique. Many of the characteristic features of human asthma were detected in those mice. They demonstrated plugging of the airway lumen with mucus as a result of goblet cell hyperplasia, shedding of the epithelium, thickening of the reticular layer beneath the epithelial basement membrane, varying degrees of airway smooth muscle hyperthrophy, and intense inflammatory cell infiltrate in the mucosa and submucosa, characterized by the eosinofilic infiltrate, but also involving lymphocyte, monocyte, and neutrophils[20].

In a recent study conducted by our group, development of peribronchial and perivascular fibrosis, inflammatory cell infiltration, goblet cell hyperplasia in the airways of BALB/c mice sensitized with OVA, according to a 48 days of sensitization and intratracheal challenge protocol was demonstrated (Fig 1)[21]. Airways were classified as small (<100μm) and large (>100μm) according to the diameter of lumen. Thickness of bronchial wall, smooth muscle and epithelium were measured for both ovalbumin and saline sensitized groups. There was no statistically significant difference in the thickness of large airways of Ovalbumin sensitized mice when compared to saline sensitized group ($p>0.1$, Mann-Whitney U Test). On the other hand, a statistically significant difference was detected in the thickness of bronchial wall, smooth muscle and epithelial layer of OVA sensitized group in small airways in comparison with the control group ($p< 0.05$, Mann-Whitney U Test). The results of this study demonstrated Goblet cell hyperplasia, subendothelial fibrosis, inflammatory cell infiltration at peribronchial and perivascular sites in Ovalbumin sensitized group but not in saline sensitized group.

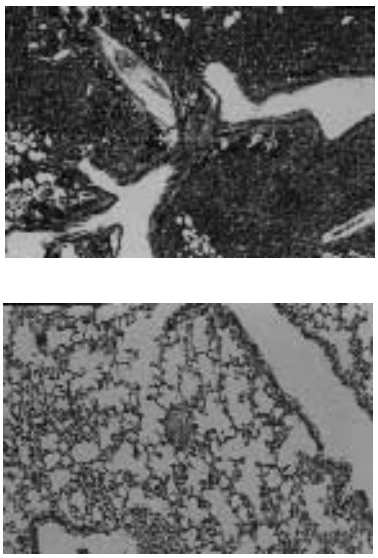

Figure 1. Comparison of the histological lung features of ova sensitised and saline treated mice. Lungs from OVA sensitized and saline group mice were obtained, fixed, sectioned, and stained with hematoxylen eosin stain. (a) In OVA sensitized mice; inflammatory cell infiltration at peribronchial site and thickness of basal membrane is seen (black arrow). Inflammatory cell infiltration is seen at perivascular site (white arrow). (b) In saline group; normal bronchial (black arrow) and vascular (white arrow) pathology is seen. (x10).

Although the exact clinical relevance of airway remodelling is not completely clear, it is proposed that treatment or preventing of remodeling is a crucial element in the management of asthma.

β2-agonists or CysLT antagonists have been shown to reduce smooth muscle proliferation in vitro[22].

The role of inhaled corticosteroids in airway remodelling needs to be better assessed. Currently available data indicate that despite these theoretical concerns, treatment with inhaled corticosteroids does not enhance tissue remodeling in established asthma. The

thickness of the reticular basement membrane is usually unchanged or slightly reduced[23]. In addition, high doses of inhaled corticosteroids significantly reduced airway vascularity. In most studies bronchial hyperreactivity improved, but did not return within normal limits, suggesting that corticosteroids cannot fully reverse remodeling.

More long-term studies are needed to appreciate the role of the prevention and treatment of remodeling. Computerized models of asthma that explore the impact of various structural alternations on airway function need to be developed.

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