# Airway remodelling in asthma and novel therapy

**Wiparat Manuyakorn,[1] Peter H Howarth[2] and Stephen T Holgate[2]**


## Summary

**Asthma is an airway inflammatory disease with functional and structural changes, leading to bronchial hyperresponsiveness (BHR) and airflow obstruction. Airway structural changes or airway remodelling consist of epithelial injury, goblet cell hyperplasia, subepithelial layer thickening, airway smooth muscle hyperplasia and angiogenesis. These changes were previously considered as a consequence of chronic airway inflammation. However, several studies have demonstrated that inflammation and remodelling can occur as separate but parallel aspects of the asthmatic process. As such there is increasing evidence for the role of mechanocompressive forces within the asthmatic airway contributing to airway structural changes. Furthermore, it is unclear what is the best treatment to modify remodelling and which component to target. There is also a need to identify asthma phenotype that might specifically respond to novel therapies such as anti-IL5, anti-IL13 and tyrosine kinase inhibitors. *(Asian Pac J Allergy Immunol 2013;31:3-10)***


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From 1. Division of Pediatric Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, THAILAND

2. Academic Unit of Clinical and Experimental Sciences and the Southampton NIHR Respiratory Biomedical Research Unit, University of Southampton Faculty of Medicine, Sir Henry Wellcome Laboratories, Southampton General Hospital, Southampton SO16 6YD, United Kingdom.

Corresponding author: Wiparat Manuyakorn

E-mail: mwiparat@hotmail.com

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## Introduction

Asthma is a common chronic disorder of the airway that is characterized by the complex interaction of airway obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation which leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The airway inflammation is typically eosinophillic and accompanied by elevation of Th2 cytokines. Eosinophils are a key feature of Th2 inflammation and are a useful biomarker in guiding treatment. However, Th2 inflammation alone cannot explain all features of asthma. For example airway hyperresponsiveness and tissue remodelling are not entirely linked to this inflammation.[1] There are a number of asthmatic patients in whom anti-inflammatory therapy does not lead to symptom control and who are considered treatment resistant. Additionally, asthmatic patients treated with an anti-IL5 mAb (mepolizumab) or T cell directed therapy that modify eosinophilic inflammation have failed to demonstrate symptomatic improvement over disease control.[1] Furthermore, whilst recognized to modify eosinophilic inflammation, inhaled corticosteroid treatment in atopic children with recurrent wheezing has been shown to have no effect on decline in lung function and the natural history of asthma over time.[2] This irreversible airflow obstruction has been shown to develop despite appropriate use of inhaled corticosteroids, as advocated by international disease management guidelines.[3] One possibility is that the decline in lung function relates to uncontrolled airway remodelling.

## Airway remodelling in asthma

Pathological repair of the airways leads to structural changes referred to as airway remodelling. Airway remodelling has been proposed to result in lower baseline lung function. Pathologically this is characterised by subepithelial thickening from increased deposition of extracellular matrix proteins (ECMs) such as collagens, proteoglycans and glycoproteins, epithelial denudation with goblet cell metaplasia, increased airway smooth muscle mass, and angiogenesis.[4] (Figure 1)

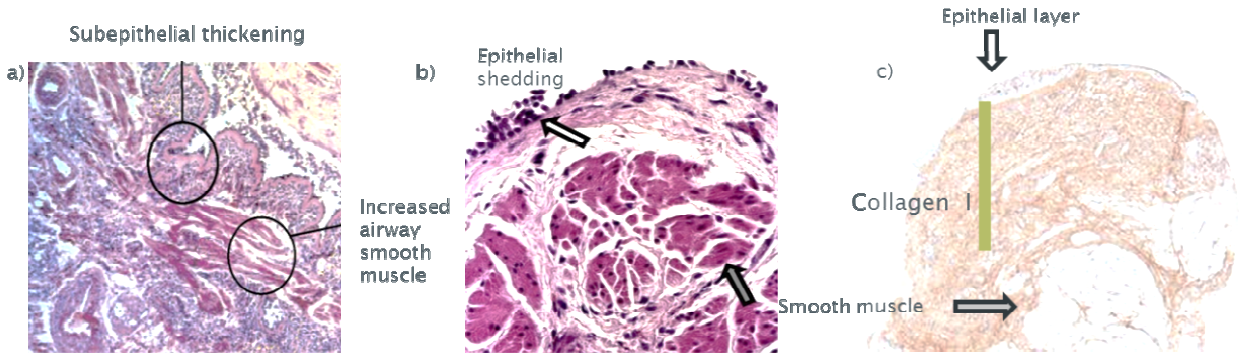


**Figure 1.** Structural changes of airway wall in asthma. Image a) and b) demonstrate epithelial shedding, subepithelial thickening and increased airway smooth muscle mass. Image c) demonstrates increased collagen deposition in subepithelial layer. Image a) and b) were reprinted from Journal of Allergy and Clinical Immunology, Vol 128, Al-Muhsen S, et al., Remodelling in asthma, Page No 453, Copyright (2011), with permission from Elsevier. Image c) was given from Dr Peter Howarth.

## Structural changes in asthmatic airway wall

### *Epithelial layer alterations*

Epithelial layer damage in asthmatic airways include shedding of the epithelium, loss of ciliated cell layer, goblet cell hyperplasia and up-regulation of several growth factors, cytokines and chemokines.[1] Previous studies have also demonstrated the change in epithelial tight junction integrity following injury.[1] However, epithelial changes are not necessarily specific to asthma as they are also observed in other airway diseases.

### *Subepithelial layer thickening*

Subepithelial layer thickening from increased deposition of extracellular matrix proteins (ECMs) is considered a characteristic feature of airway remodelling in asthma. Subepithelial basement membrane thickening is confined to the *lamina reticularis* (reticular basement membrane - RBM). The true basement membrane, consisting of the *lamina rara* and *lamina densa*, divides the airway epithelium from the mesenchyme and is not altered in thickness in asthma. Roche et al. has shown that this thickened subepithelial basement membrane consists of a dense layer of fibrillar collagens.[5] Immunohistochemistry revealed that the thickened reticular layer is largely composed of collagen I, III and V and fibronectin.[5] The distribution of laminin and collagen IV is unaltered in asthma. Collagen I was also localised in the interstitium of the submucosal layer through the muscular layer.[5] Collagen IV is the major constituent of the true basement membrane. The major cells that are responsible for ECMs production in the airway are fibroblasts and myofibroblasts. Inflammatory cells, such as mast cells, eosinophils, and T cells, also accumulate in the submucosal layer, where the fibroblasts/myofibroblasts are situated. The interaction between inflammatory cells, structural cells (e.g. epithelial cells and fibroblasts) and the turnover rate of extracellular matrix proteins (ECMs) determines the net balance of remodelling and fibrosis within the airways. This may suggest an essential role for fibroblasts/myofibroblasts in communicating inflammatory signals from the epithelium through the airway wall. Therefore, the chronically injured epithelium and improper repair may contribute to the thickening of the *lamina reticularis* in the asthmatic airways. It has been shown that epithelial cells release growth factors, such as TGF-β in response to damage that directly influence the synthesis of matrix proteins by fibroblasts/myofibroblasts.[6] As a result, this leads to the concept of the epithelial mesenchymal trophic unit (EMTU) as an integrated component within the airways of relevance to asthma.

Subepithelial layer thickening also has shown to associate with asthma severity. However, there is no evidence of association with asthma duration both in fatal and stable asthma studies.[7] Apart from evaluating airway wall thickness using biopsy samples, high-resolution computed tomography (HRCT) has been used to measure the internal size of the airways. The airway wall thickness as assessed by HRCT in the asthmatic airway was demonstrated to inversely correlate with airway hyperresponsiveness.[8] Additionally, asthmatic patients who have highly variable airway obstruction or brittle asthma has been shown to have a less airway wall thickening, while those who had

less variable or fixed airway obstruction exhibited more thickened airways.[9] It was proposed that the thickening with deposition of the matrix proteins may exert a protective mechanism by increasing the stiffness of the airways to attenuate the sporadic bronchoconstriction.[1]

***Airway smooth muscle hyperplasia and hypertrophy***

Smooth muscle layer in the airways is increased by 50-200% in fatal asthma and 25-55% in non-fatal asthma, compared with normal subjects.[10] These changes could be from smooth muscle cell hyperplasia, hypertrophy or increased ECMs between cells and contributing to airway narrowing from excessive airway smooth muscle shortening during contraction which is most likely responsible for the pathophysiology of airway hyperresponsiveness in asthma. Asthmatic subjects with increased airway smooth muscle (ASM) confined to the large airways have predominately ASM hyperplasia whereas those cases with increased airway smooth muscle in both the large and small airways had hypertrophy and some hyperplasia in the large airways.[11] Furthermore, the migration of ASM cells toward the epithelium has been suggested as one feature of airway remodelling in asthma.[12] ASM cells are biologically active and may participate in the remodelling process through the synthesis of ECMs in response to growth factors (TGF-β, VEGF, and CTGF) and serum from asthmatic patients.[13] Increased airway smooth muscle mass has been suggested to be responsible for the pathophysiology of airway hyperresponsiveness.

***Angiogenesis***

Angiogenesis, the formation of new blood vessels from pre-existing ones, has been observed mainly below the basal lamina in the space between the muscle layer and the surrounding parenchyma in remodelled airway of asthmatic patients.[12] This change results in increased vascular area in the medium and small airways, increased blood flow and microvascular permeability and predisposes to oedema formation. These latter processes will most likely contribute to the thickness of the airway wall although it is difficult to quantify *in vivo*. Vascular endothelial growth factor (VEGF) has been shown to be involved in these abnormalities.[14] A recent study has also proposed a role for tissue factor (TF), a primary initiator of blood coagulation, secreted by bronchial epithelium after mechanical stress on angiogenesis of asthmatic airway.[15]

***Airway inflammation and airway remodelling***

Traditionally airway remodelling has been linked to airway eosinophilic inflammation as these cells can generate the pro-fibrotic growth factor TGF-β. However, there are a number of lines of evidence that question the dependence of this process, either in part or entirely, on eosinophils. Structural remodelling of the airways has been found in children with recurrent wheezing regardless their atopic status.[16] It has also been reported that airway epithelial cells in asthmatic children express makers of injury, such as the epidermal growth factor receptor (EGFR), one of the receptor tyrosine kinase, even in the absence of significant eosinophilic inflammation.[17] A recent study has also demonstrated increased RBM thickness in severe asthmatic children without the evidence of Th2 inflammation.[18] These studies suggest that remodelling can occur independently of Th2 inflammation. Furthermore, evidence of airway remodelling, such as epithelial layer damage, thickening of basement membrane, angiogenesis has been demonstrated in children as early as 4 years of age in asthmatic subjects.[16] It is thus an early feature of the disease and not only a marker of long standing chronic disease. However, the subepithelial thickening has not been demonstrated in wheezer infants.[19] This indicates that airway thickening begins early in the development of asthma and may play role in the disease progression in some patients.

***Physical forces and airway remodelling***

Human airways are exposed to a range of physical forces that may potentially arise in several ways, such as during inspiration-expiration, cough and bronchoconstriction from airway smooth muscle contraction during asthma exacerbation. The major structural cells of the airways (epithelial cells. fibroblasts, and smooth muscle cells) are responsible for these physical stimulations. Airway smooth muscle contraction produces a compressive stress on the airway epithelium, fibroblasts and smooth muscle itself. Therefore, abnormal physical loading to the airways may result in altered cellular activations and modify the composition of ECMs leading to airway structural changes or airway remodelling. Several previous *in vitro* studies have demonstrated the role of physical forces on airway structural cells responses involved in airway remodelling: increased cell proliferation[20], increased deposition of ECMS and subepithelial layer thickness[21], promoted smooth muscle cells migration[22], production of contractile enzyme and

VEGF.[23] This was supported by a recent *in vivo* study which has shown increases in collagen deposition in the subepithelial layer, mucus secreting goblet cells and cell proliferation in both subepithelial layer and submucosal layer after bronchoconstriction using methacholine challenge, a stimulus that did not affect airway inflammation. Additionally, airway wall thickening has been observed in patients with cough variant asthma and non-asthmatic chronic cough.[24] These studies provide new important insights on the impact of physical forces on pathogenesis of airway remodelling in asthma.

## Current asthma medication and airway remodelling

### *Inhaled corticosteroids (ICS)*

Inhaled corticosteroids are suggested as currently the most effective anti-inflammatory medications for the treatment of chronic asthma. Even though inhaled corticosteroids have been shown to reduce asthma symptoms and exacerbations, they have failed to alter the natural history of disease, at least in children. Thus, treatment atopic children with recurrent wheezing using inhaled corticosteroids have shown no effect on decline in lung function or the natural history of asthma.[2] The role of corticosteroids in reversing airway remodelling remains controversial. There is evidence of an increase in the number of ciliated bronchial epithelial cells after 3 months of high dose budesonide treatment.[25] However, it was found that asthmatic subject airway smooth muscle mitogenesis and growth were resistant to glucocorticoids *in vitro.*[26] Several studies have examined the effect of corticosteroids on subepithelial collagen thickness but the results are inconsistent depending upon the steroid dose and duration of administration. High dose ICS (1000-3000 mcg/day of budesonide equivalent) with a duration of treatment of more than 6 months has been reported to be associated with a reduction in subepithelial collagen thickness.[27] By contrast, there is no change in subepithelial collagen thickness with low dose ICS or short duration of treatment.[27] The doses needed to affect a change are thus beyond the dose clinically used by many patients. Consistent with such a consideration, high dose fluticasone propionate (1000 mcg/d) has been demonstrated to decrease vascular-associated remodelling.[28] However, the use of such high doses would have to be considered in relationship to the potential for adverse effects and there are several studies demonstrating an effect of inhaled steroids in children on growth. While there are many studies showing the ICS can impair skeletal growth in childhood, recently this has been shown to an effect on adult height.[29] In addition, it was shown that ICSs cannot prevent the declining of lung function in asthma or prevent the progression of asthma in high risk young children.[2]

### *Inhaled corticosteroids plus long acting beta2 agonist*

Although, the combination of ICS and long acting β2 agonist (LABA) are widely used in moderate to severe asthma, their ability to modulate airway remodelling is not well established. *In vitro* studies have demonstrated that LABA (salmeterol and formoterol) and the combination of corticosteroids and LABA suppressed collagen production by lung and airway fibroblasts, but the opposite effects were shown in fibroblasts treated with fluticasone or budesonide, the commonly used inhaled corticosteroid.[30] Formoterol-budesonide has been shown to decrease subepithelial layer thickness in asthmatic subjects.[31] This was attributed to an additional anti-inflammatory action of the combination but another interpretation is that it is related to its anti-bronchoconstrictor influence protecting against airway mechanotransductive effects.

### *Leukotriene receptor antagonists*

Current asthma guidelines also recommend leukotriene receptor antagonists as alternative controller therapy for chronic asthma. Therefore, it is of interest that montelukast, leukotriene receptor antagonist, has been shown to reduce subepithelial layer thickening in a mouse asthma model.[32] However the effect of montelukast on airway remodelling in asthmatic subject need to be further investigated.

### *Anticholinergics*

Anticholinergics are commonly used for the treatment in chronic obstructive pulmonary disease and in asthma primarily as a bronchodilator. Recent studies in mouse model of chronic asthma have shown the ability of tiotropium, a long acting anticholinergic receptor drug targeting on muscarinic M3 receptor subtype, to inhibit airway remodelling. Tiotropium has been demonstrated to decrease airway goblet cell metaplasia, thickness of airway smooth muscle, and airway fibrosis in treated mice.[33] The addition of tiotropium to asthma poorly

controlled with standard combination therapy has been demonstrated to significantly increase the time to the first severe exacerbation.[34] However, the effect of tiotropium on airway remodelling has not been evaluated.

***Omalizumab***

Omalizumab is a recombinant humanized IgG1 mAb that recognizes the Fc portion of free IgE to prevent its attachment to the high-affinity receptor for IgE of mast cells, basophils, and dendritic cells. This action decreases circulating IgE levels, which in turn down-regulates IgE receptor expression resulting in blocking the early allergic cascade inflammation. Apart from its anti-inflammatory effects, omaluzumab has been shown to reduce airway wall thickness in severe asthmatic subjects as evaluated by HRCT[35] and decrease reticular basement membrane thickness in bronchial biopsies.[36] As a result, omalizumab may have a potential role on airway remodelling in severe persistent allergic asthma.

**Novel treatment on airway remodelling**

***Vitamin D***

There is an increasing evidence of the association of vitamin D deficiency and asthma severity. In vitro studies have shown that vitamin D has a role on ASM remodelling by inhibition on ASM growth.[37] Low levels of vitamin D in moderate-severe asthmatic children has been shown to be associated with poorer lung function, the requirement for higher dosage of ICSs, a greater tendency for asthma exacerbations and an increase in the thickness of airway smooth muscle but not to be associated with airway epithelial shedding or reticular basement membrane thickness.[38] Vitamin D supplementation may thus theoretically have a beneficial role on asthma control and airway remodelling, especially on airway smooth muscle thickness, but this has yet to be conclusively demonstrated.

***Anti-IL-5***

IL-5 promotes terminal differentiation, bone marrow release, and survival of eosinophils. It was shown that mepolizumab decreased the number of tissue eosinophils, the deposition of extracellular matrix proteins (tenasin, lumican, and procollagen III) in bronchial RBM, eosinophil and the level of TGF-β1 in BALF of mild atopic asthma.[39] Two recent studies of mepolizumab in prednisolone dependent asthma with sputum eosinophilia demonstrated that mepolizumab significantly reduced exacerbation rates[40, 41] and a small but significant improvement in $FEV_1$ with mepolizumab in one study.[41] In another there was a significant improvement in the airway wall thickness when evaluated HRCT.[40] These small studies suggest that anti-IL-5 may have a role on airway remodelling in selected patient populations. The lack of effect of mepolizumab on lung function in a large multicenter study does suggest that, if treatment with this biologic has an effect; it is not consistent in severe asthma and may be confined to as yet undefined sub-populations.[42]

***Anti-IL-13***

Interleukin-13, a pleiotropic cytokine of type 2 helper T cells, has been demonstrated to involve in IgE isotype switching, eosinophilic airway inflammation and airway remodelling in asthma. IL 13 in the airways enhances the survival and migration of eosinophils, increased mucus production by airway epithelial cells. It also promotes the transformation of airway fibroblasts to myofibroblasts, leading to increase collagen production which is responsible for the thickening of bronchial walls due to subepithelial fibrosis in the airways.[43] Lebrikizumab, a humanized mAb that specifically binds to and inhibits the activity of IL-13, has been shown to improve $FEV_1$ in patients with uncontrolled asthma especially in patients who had high periostin, an extracellular matrix protein that is secreted by airway epithelial cells and lung fibroblasts after stimulation with IL-13 and IL-4.[44] Periostin has been demonstrated to associate with subepithelial fibrosis in asthmatic subject.[44]

***Anti-TNFα***

TNFα, an important cytokine in the innate immune response, is secreted by macrophage, inflammatory cells and airway structural cells (i.e. epithelial cells, fibroblasts and smooth muscle cells). TNFα has been suggested to have a role on severe refractory asthma and airway remodelling, including, recruitment of neutrophils, induction of glucocorticoid resistance, stimulation of fibroblast growth and myofibroblast differentiation, increase myocyte proliferation, and was proposed to have a role in airway remodelling in asthma.[45] Initial small studies of anti TNFα, with the soluble TNFα fushion protein eternacept, found a decrease in BHR and improved lung function in severe asthma.[46] These findings were, however, apparently contradicted by a later large multicentre study of golimumab, a mAb

against TNFα, which failed to influence either lung function or exacerbation rate. However, a post-hoc sub-population analysis reported that patients with reversible airway obstruction had a decrease in exacerbations.[47] Therefore, this finding would suggest that patients with fixed airway obstruction or airway remodelling may be a phenotype that is less response to anti-TNFα.

### *Tyrosine kinase inhibitors*

Several receptor tyrosine kinases, including epidermal growth factor receptor (EGFR), c-kit (a stem cell factor receptor), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR) and non receptor tyrosine kinases, including spleen tyrosine kinase (Syk), Src, and janus kinase (JAK), have an important roles in asthma. Their ligands are primary growth factors that are responsible for repair and remodelling in asthmatic airways. Currently there are both *in vitro* and *in vivo* studies in animal regarding these tyrosine kinase inhibitors and airway remodelling in asthma.[48] EGFR inhibitor has been shown to reduce airway smooth muscle and epithelial cell proliferation, decrease collagen deposition and goblet cell proliferation.[48] A PDGRF inhibitor has been shown to diminish smooth muscle cell proliferation *in vitro*.[49] Administering c-kit inhibitor to asthma animal models has also been shown to improve lung compliance and decrease eosinophilic airway inflammation.[50] Syk, Src and JAK inhibitors have been shown to attenuate bronchial smooth muscle contraction, reduced airway inflammation and edemal.[48] However, there are so far no studies which have translated these findings to clinical applicability in asthma due to the complex nature of disease.

## Conclusions

Airway remodelling in asthmatic subjects arising from injury and repair is a multicellular processes resulting in airway structural changes that contribute to pathophysiology, progression of airflow obstruction and treatment responsiveness. The failure of treatment targeting airway inflammation, such as inhaled corticosteroids, to modify the natural history of lung function changes in asthma, at least in children, highlight the need for continued exploration on the mechanisms responsible for these structural changes. There are also mixed phenotypes of asthmatic subjects, which may have different changes in the area of remodelling. Phenotypes specific treatment by classification of asthmatic patients into inflammatory, clinical, molecular, or genetic sub-phenotypes may have the potential to guide therapeutic decision making for the management of asthma and prevent for the progression to remodelling.

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