



Airway remodeling in asthma: update on mechanisms and therapeutic approaches

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Purpose of review

The term 'airway remodeling' reflects changes in the type, quantity, and nature of airway wall components and their organization. The purpose of this review is to look at recent publications on airway remodeling in asthma.

Recent findings

Animal models and in-vitro studies have confirmed the involvement of airway epithelium, airway smooth muscle (ASM), and extracellular matrix components in asthma-related airway remodeling. They report influences on proliferation of ASM cells, and how their orientation or morphology, in addition to the heterogeneity of ASM mass at different levels of airways could influence their effects. Clinical benefits have been observed following reduction of ASM following bronchial thermoplasty. Asthmatic epithelial cell transcriptome alterations were found to involve metabolism and epigenetics, beyond epithelial mesenchymal trophic unit driven by injury and repair in chronic inflammation. New ways to explore airway remodeling such as imaging or endoscopic techniques have been evaluated. Finally, new data support the role of eosinophils and mast cells in remodeling and show the influence of new asthma drugs on this process.

Summary

As recently stated by an American Thoracic Society task force, we need more research on airway remodeling, its determinants and clinical relevance, and on the effects of asthma drugs on its various components.

Keywords

airway hyperresponsiveness, airway remodeling, asthma

INTRODUCTION

Airway remodeling can be defined as a set of changes in the composition, content, and organization of the cellular and molecular constituents of the airway wall [1]. This could constitute a normal development or repair process, such as during lung development, aging, or as a transient response to airway/lung injury, with restoration of normal structures. However, it can also be pathological, such as in response to chronic injury/inflammation, resulting in persistently altered airway structure and function. In asthma, airway remodeling has been typically considered as a result of a bronchial inflammatory insult either from allergen exposure in sensitized patients or other environmental hazards [2], although mechanical stress may be involved [3] or it may result from early life events [4]. Typical structural asthmatic changes include epithelial damage, mucus gland hyperplasia, subepithelial basement membrane deposition of collagen and proteoglycans, angiogenesis, and increases in airway smooth muscle (ASM) mass [1].

Despite evidence that inflammation is involved in airway remodeling, these two processes seem to evolve in parallel, although they do not always correlate well. Changes in structural cells could also influence inflammation and other components of remodeling [5–7]. Airway remodeling can be observed without associated airway hyperresponsiveness (AHR) or evidence of symptomatic asthma, such as in allergic rhinitis or in high-level athletes [8,9], and it can significantly increase when asthma develops in atopic patients [10]. Airway remodeling is usually considered detrimental (Table 1) [11–13]. However, it could also have some protective effects

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KEY POINTS

- Structural changes occur in the airways of patients with asthma and may be responsible for alterations in airway hyperresponsiveness and the development of a fixed component of airway obstruction.
- Although the pathophysiology of airway remodeling remains to be elucidated, airway inflammatory cells such as eosinophils and mast cells along with other factors may play a major role in its development.
- Existing asthma drugs have a limited effect on many features of airway remodeling.
- The influence of new monoclonal antibodies on airway remodeling, and the possibility that they may alter the course of the disease, needs further evaluation.
- Bronchial thermoplasty reduces the thickness of airway smooth muscle and may alter other components of airway remodeling.
- Airway remodeling is a valid treatment target and thus research in this field should be facilitated and promoted.

[14]. Consequently, airway remodeling is a complex process with multiple components that may have different effects on airway function and this remains to be studied.

In regard to how structural changes could lead to AHR, increases in ASM mass, angiogenesis, and ECM/collagen deposition within the airway has been the subject of recent reviews. First, Lauzon *et al.* [15[¶]] summarized the potential role of ASM as a key-factor of AHR. ASM is indeed increased in many patients with asthma and interleukin (IL)-13

Table 1. Possible detrimental or beneficial effects of airway remodeling

Possible detrimental effects of airway remodelling
Contribution to the decline in lung function
Development of an irreversible component of airway obstruction
Reduction of airway distensibility and of bronchodilator response
Development and persistence of airway hyperresponsiveness
Loss of protective smooth muscle stretch relaxation
Increased contractile response from ASM mass increase and amplifying mechanisms
Loss of lung elastic recoil
Possible beneficial effects
Protection against maximal bronchoconstriction
Prevention of airway collapse from airway wall stiffening

and tumor necrosis factor (TNF)- α promote a more contractile ASM phenotype. Composition and the increased stiffness of ECM in which ASM is embedded seem to promote a more proliferative and pro-inflammatory ASM phenotype. Airway epithelium may also drive ASM proliferation and remodeling. Otherwise, Poon *et al.* [16] suggested that angiogenesis and mucosal neovascularization are key features of airway remodeling in severe asthma. Finally, in regard to ECM and collagen deposition, reports suggest that deposition of proteoglycans or collagen in the airway wall can contribute to AHR [17,18].

Although there are significantly less research performed on airway remodeling compared to airway inflammatory processes, recent data have shed light on its underlying mechanisms, its noninvasive assessment, its potential role in asthma therapy, and the influence of asthma therapies on its components. Prakash *et al.* [19[¶]], reporting the proceedings of a new task force of the American Thoracic Society on Airway Remodeling, stressed the need for more research in airway remodeling and for developing, testing, and ultimately improving drugs that target this phenomenon.

PATHOGENESIS OF AIRWAY REMODELING

In-vitro models

The epithelial mesenchymal trophic unit (EMTU) concept has been proposed to explain the development of airway remodeling following airway insults [20]. Recently, Bucchieri *et al.* developed an in-vitro model mimicking the EMTU of the bronchial mucosa that could be useful to study of pathogenesis of lung diseases such as asthma and COPD [21[¶]]. They developed a bronchial mucosal model of bronchial tissue embedded in Matrigel and obtained outgrowth cultures. These latter formed a multicellular sheet with motile cilia becoming evident as the Matrigel was remodeled to provide an air interface. Extracellular matrix (ECM) interspersing with fibroblastic cells separated by a basement membrane was observed. Repeated exposure to cigarette smoke extract caused epithelial damage, loss of cilia, and ECM remodeling.

Similarly, using tissue engineering, we previously developed a bi-dimensional model of bronchial cells obtained from bronchial biopsies; it presented a pseudostratified ciliated epithelium with the presence of mucus secretory cells, although the tissue structure was disorganized [22]. These models could be useful to study airway remodeling in the pathogenesis of lung diseases such as asthma and COPD and the effects of various exposures or drugs.

Furthermore, recent reports deal with in-vitro study of ASM function and influences on its proliferation. Using a porcine ASM strips in-vitro model, Dogan *et al.* [23] suggested that tumor necrosis factor (TNF) increases force generation of ASM by increasing the number of contractile units (actin–myosin content). Also, using cell cultures of ASM, Januskevicius *et al.* [24] reported that blocking eosinophil–ASM interactions through RGD-binding integrins with small tetrapeptide Arg-Gly-Asp-Ser attenuated eosinophil-induced ASM remodeling in asthma.

A study reported by Ljpmma *et al.* [25] examined the role of ASM orientation and morphology as determinants of the ability of the muscle to constrict the airway. Dissected human airway trees from patients with asthma and control lungs were stained, intact airway sections were imaged in axial projection to show ASM bundle orientation, and cross-sectional histological slides were produced. ASM mass increase in cartilaginous airways was primarily the result of an increase of ASM bundle thickness as measured radially in an airway cross section. ASM orientation was unchanged in all airways.

According to Pascoe *et al.* [26], previous modeling studies have suggested that the increase in ASM mass had the largest effect on increasing maximal airway narrowing. Using measurements made on histological sections from donor lungs, they showed that there is marked heterogeneity of ASM area and wall area in both patients without asthma and patients with asthma. Using a mathematical model, they determined that this heterogeneity contributed to an increased baseline resistance and elastance in patients with asthma and a leftward shift in the responsiveness of the airways to an agonist in both groups, the latter being mainly because of an increased susceptibility for the small airways to close.

Furthermore, Movassagh *et al.* [27] examined the molecular mechanisms controlling ASM cell proliferation. They reported that a semaphorin 3A (Sema3A) receptor, neuropilin 1 (Nrp1), is expressed on human ASM cells (HASM) isolated from healthy and asthmatic donors and that treatment of these cells with exogenous Sema3A inhibited growth factor-induced proliferation. Their data suggest Sema3A–Nrp1 signaling as a novel regulatory pathway of ASM hyperplasia.

Finally, Loffredo *et al.* [28] examined the epithelial-to-mesenchymal transition (EMT) in asthma. They used unbiased gene network analysis to evaluate functional convergence in epithelial gene expression signatures. They demonstrated a marked suppression of epithelial differentiation in asthma. They also identified novel markers, central to dysregulation of epithelial–mesenchymal signaling.

This ‘core’ signature of asthma was present in all severities of asthma but progressing with severity. The authors conclude that epithelial barrier dysfunction in asthma is characterized by persistent de-differentiation program with complex etiology and that the lasting alteration of the asthmatic epithelial cell transcriptome implicates regulation involving metabolism and epigenetics, beyond EMT driven by injury and repair in chronic inflammation.

Animal models

Gonzalez-Avila *et al.* [29] explored collagen metabolism in airway tissues from guinea pigs in acute (35 days) or chronic (125 days) experimental models of atopic asthma using ovalbumin challenge. They observed an increase in collagen deposition in bronchioles basement membrane, adventitial and ASM layers lung tissue collagen concentration in both experimental models. These structural changes persisted 1 month after the last challenge.

Human studies

In regard to the influence of inflammatory cells on airway remodeling in asthma, a recent study by Inoue *et al.* [30] supports the role of eosinophils in inducing remodeling. They studied 26 patients with eosinophilic asthma (sputum eosinophils >3%) and 37 patients with noneosinophilic asthma (NEA). The eosinophilic asthma group had, in addition to a significantly longer asthma duration and lower pulmonary function, a higher fractional exhaled nitric oxide (FeNO) and higher percentage of wall area (WA%, airway wall area/outer area of the bronchus $\times 100$) and smaller airway luminal area compared to the NEA group. Sputum eosinophil differential counts and WA% were positively correlated.

Naveed *et al.* [31] showed that in patients with asthma, airway pro-matrix metalloproteinase-1 was 5.4-fold higher than in control patients, and mast cell numbers were associated with ASM proliferation whereas MMP-1 protein was associated with AHR. The authors conclude that MMP-1 is activated by mast cell tryptase, resulting in a pro-proliferative extracellular matrix and that ASM/mast cell interactions can contribute to asthma severity by transiently increasing MMP activation, ASM growth, and AHR.

ASSESSMENT OF AIRWAY REMODELING

Airway remodeling is more difficult to assess than airway inflammation, for which noninvasive measures have been developed such as induced sputum

analysis and FeNO measurement. Bronchial biopsies are only done in research settings. Postbronchodilator airway function may reflect airway remodeling, but there is a search for biomarkers that could reflect this process. Some of these have been suggested, such as measures of the ratio of tissue inhibitor of matrix metalloprotein/matrix metalloprotein 9 (TIMP/MMP9) in sputum supernatants or blood fibrocytes but these are imperfect markers. Developments of imaging techniques are promising [30[¶]]. Quantitative computed tomography (QCT) imaging of the tracheobronchial tree and lung parenchyma allow investigators to study large airway structure and assess indirectly small airway structure from expiratory gas trapping measurements [32].

Biomarkers and high-resolution computed tomography

Clinicians and researchers would appreciate to have a simple and noninvasive marker of airway remodeling [33]. Periostin is a protein expressed in epithelial and matrix cells that is upregulated by T2 cytokines including IL-4 and IL-13 and is implicated in basement membrane fibrosis. Hoshino *et al.* investigated the relationships between high-resolution computed tomography (HRCT) measurement of airway wall thickness and serum periostin in corticosteroid naïve patients with asthma. Serum periostin correlated with airway wall thickness and both decreased with inhaled corticosteroid treatment in parallel with a fall in sputum eosinophils [34].

Gorska *et al.* examined bronchial wall thickness (BWT) assessed with HRCT and endobronchial ultrasound (EBUS) in mild-to-moderate asthma and chronic pulmonary obstructive disease (COPD). There was a good overall agreement between EBUS and HRCT measurements of BWT and no significant differences between individuals with asthma, COPD, and control patients on HRCT. In contrast, median BWT measured by EBUS was significantly higher in asthma and COPD groups when compared with controls [35].

Hartley *et al.* compared thoracic quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema between patients with asthma and COPD and explored their relationship with airflow limitation. Proximal airway percentage wall area (%WA) was significantly increased in patients with asthma and COPD compared with healthy controls, as did air trapping, assessed from mean lung density expiratory/inspiratory ratio. Emphysema, assessed according to lung density, was a feature of COPD only. The strongest predictor of lung function impairment in patients

with asthma was WA%, whereas in patients with COPD and those with asthma with less than 80% forced expiratory flow in one second (FEV₁) percentage predicted value, it was air trapping [36].

Endoscopic techniques

New endoscopic techniques may help assess airway remodeling. In this regard, Ding *et al.* used endobronchial optical coherence tomography (EB-OCT) to assess staging of COPD and the association between disorders of large and medium to small airways in these patients and evaluated small airway architecture in heavy smokers with normal FEV₁ (S_{NL}) and healthy never-smokers [37]. Patients with more advanced COPD demonstrated greater abnormality of airway architecture in both large and medium to small airways, followed by S_{NL} and never-smokers. These techniques are of interest to evaluate airway architecture in asthma.

Forced oscillation technique

A noninvasive index of airway distensibility could be useful as a surrogate markers of airway remodeling. Forced oscillation technique (FOT) provides such an index by measuring the change in respiratory system conductance over the corresponding change in lung volume. In this regard, Mailhot-Larouche *et al.* [38] confirmed the reproducibility of airway distensibility measurements by FOT and suggested a simplified method to increase feasibility.

TARGETING AIRWAY REMODELING

Inhaled medications

The influence of asthma medications on airway remodeling has been previously reviewed [39,40]. Inhaled corticosteroids help restore epithelial integrity and can prevent vascular changes and ECM matrix components deposition in airways, but their effect on collagen deposition is limited. In animal models, leukotriene receptor antagonists and anticholinergics were shown to influence airway remodeling features such as goblet cell metaplasia, thickness of ASM, and airway fibrosis, but if these effects also happen in humans remain uncertain [41].

Bronchial thermoplasty

Although it remains unclear which component of remodeling should be targeted to provide optimal benefits, recent studies on bronchial thermoplasty brought new data on this issue.

Pretolani *et al.* [42] and Chakir *et al.* [43] showed that bronchial thermoplasty significantly reduced ASM area and improved asthma control. Pretolani *et al.* [42] demonstrated that the reduction in ASM area correlated with the improvement in asthma control, quality of life and the decrease in severe exacerbations, hospitalizations, and visits to the emergency department for asthma at 3 and 12 months, whereas Salem *et al.* [44] showed BT-induced ASM and RBM thickness reduction, and that clinical benefits persisted 27–48 months after treatment.

Monoclonal antibodies

Furthermore, the new monoclonal antibodies developed for asthma therapy may act on remodeling processes, either directly or in influencing key inflammatory mechanisms [45]. Tyrosine kinase inhibitors and some anticytokines can also modulate airway remodeling, including those targeting IL-5 (e.g. mepolizumab), IL-13 (e.g. lebrikizumab), and TNF- α . However, the magnitude and clinical impact of the effect of these agents needs to be further studied. Previous studies had shown a potential for anti-IL-5 to influence remodeling such as reduction of expression of proteoglycans in the airway wall [46]. However, more studies need to be done on the anti-remodeling effects of these molecules.

Riccio *et al.* [47] recently looked at histological and molecular effects of 36 months treatment with an anti-IgE on bronchial biopsy specimens. There was a reduction of reticular basement membrane (RBM) thickness in omalizumab responders (Galactin-3-positive at baseline). Similarly, in the responders group, levels of proteins specifically related to fibrosis and inflammation, including periostin, Galactin-3, and keratins, decreased by between 5-fold and 50-fold with omalizumab. Eosinophil levels decreased by about tenfold less in responders whereas it increased in nonresponders. The authors suggest that Galactin-3 could be a biomarker of remodeling, eosinophilia, and muscular and fibrotic components, in omalizumab-treated patients with severe asthma.

Other molecules

Lee *et al.* recently showed that the drug Nintedanib, used in pulmonary hypertension, improved airway inflammation and remodeling such as goblet cell hyperplasia, total lung collagen level, and ASM area, in an ovalbumin-induced chronic asthma model, and that this drug could be a potential new treatment agent targeting airway remodeling in patients with severe asthma, although it remains to be determined if this applies to humans [48].

PREVENTION OF REMODELING

Early interventions to prevent remodeling may possibly help prevent the development of asthma but much remains to be studied about this possibility [49,50]. However, we still do not know how efficiently prevent airway remodeling. We are probably intervening too late; however, as a large part of airway remodeling seems to happen before the development of symptomatic asthma or early in life [8,51]. An analysis of airway remodeling in fatal pediatric and adolescent asthma recently found an increased thickness of the reticular basement membrane, numerous eosinophils, and mucous plugs, even in small airways, in children and adolescents with fatal asthma but increased ASM was detected in only one third of the patients [52]. Features of remodeling may vary according to age and type of asthma.

Cessation of exposure to environmental sensitizers can lead to a mild reduction in airway remodeling. Animal models and human studies have shown a prevention or reduction of some airway remodeling features with corticosteroids, although these changes are usually modest [18,53]. We therefore need to explore other means of preventing more efficiently airway remodeling.

CONCLUSION

Asthma-related structural changes are complex. Much remains to be known on how, why airway remodeling develops in asthma and how these changes contribute to alterations of airway function. Studies should be conducted to determine possible benefits of asthma treatments in influencing these processes. Furthermore, we should explore if prevention of airway remodeling could prevent the development of asthma in at-risk patients and determine if its reduction could contribute to asthma remission or reduction in severity. Until we obtain additional data, airway remodeling remains a valid treatment target.

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