Review Article

Research advances in airway remodeling in asthma: a narrative review

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Background and Objective: Asthma is a common chronic disorder of the airway, and its disability and mortality rates continue to increase each year. Due to the lack of an ideal treatment, asthma control in China remains unsatisfactory. Airway remodeling is the pathological basis for the eventual development of the fixed airflow limitation in asthmatic patients. Early diagnosis and the prevention of airway remodeling has the potential to decrease disease severity, to improve control, and to prevent disease expression.

Methods: This article presents an overview. The literature was combed through via CNKi and PubMed according to the listed keywords. We considered Chinese and English original publications (basic science and clinical), reviews and abstracts of 21th Century.

Key Content and Findings: We review the pathological features and pathogenesis of, and the interventional treatment options for airway remodeling in asthmatic patients, emphasizing the importance of airway remodeling in asthma and providing novel insights into the prevention and control of asthma.

Conclusions: Thus, there have been research advances in airway remodeling, especially in the areas of slowing down or reversing airway remodeling. As growing studies showed, treating airway remodeling is a promising strategy in preventing the occurrence and progression of asthma. Breakthroughs in these difficulties airway remodeling still facing will open up new avenues in the research and treatment of asthma.

Keywords: Asthma; airway remodeling; pathological features; treatment

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Introduction

Bronchial asthma, commonly known as asthma, is a heterogeneous disorder characterized by chronic airway inflammation, airway hyperresponsiveness, and reversible airflow limitation. The long disease course may result in a series of structural changes in the airway, known as airway remodeling. Airway remodeling is the pathological basis for the eventual development of fixed airflow limitation in asthmatic patients. Traditionally, airway remodeling was thought to occur secondary to chronic inflammation. However, there is growing evidence (1,2) that airway remodeling co-occurs in conjunction with chronic inflammation, which explains the clinical occurrence of irreversible or partially reversible airflow limitation in some asthmatic patients despite the use of anti-inflammatory drugs and bronchodilators. The progressive development of airflow obstruction in asthmatic patients leads to complex and diverse clinical presentations that are difficult to treat. Clinically, nowadays no drug can inhibit airway remodeling (3). In recent years, studies (3-15) have focused on the mechanism of airway remodeling in asthmatic patients and the potential therapeutic targets that may enable the early blockage or even the reversal of the airway

Table 1 The search strategy summary

Items	Specification
Date of search	2022-05-30
Databases and other sources searched	CNKI and PubMed
Search terms used	Asthma, airway remodeling, pathological features, treatment, *et al.* (see the independent Table S1 below to present detailed search strategy of PubMed as an example.)
Timeframe	2001-03 to 2022-07
Inclusion criteria	Chinese and English original publications (basic science and clinical), reviews and abstracts
Selection process	The authors obtained consensus after analysis independently

remodeling process. In this review article, we summarize the pathological features and pathogenesis of airway remodeling, the effects of airway remodeling on asthma, and the intervention options for airway remodeling in asthma, providing novel insights into the prevention and control of asthma. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2835/rc).

Methods

This article presents an overview. The search strategy summary see *Table 1* for details.

Concept of airway remodeling in asthma

Airway remodeling can be either pathological or physiological. Asthmatic airway remodeling refers to changes in the structures, constituents, and functions of airway wall cells due to airway inflammation, tissue injury, and subsequent over-repair processes in asthmatic patients relative to normal individuals. It can occur in both large and small airways, and its principal morphologic features include epithelial disruption, subepithelial fibrosis, smooth muscle hyperplasia, glandular hypertrophy, and neoangiogenesis (16). These changes eventually lead to airway wall thickening, airway narrowing, and airway hyperresponsiveness (17-19).

Pathological features of airway remodeling in asthma

Repeated asthma flare-ups over a long period cause pathological changes in the normal airway structure. A variety of cells and cellular components are involved in the airway damage-repair-damage-repair processes, resulting in airway remodeling, which is an important pathophysiological feature of asthma. The main pathophysiological manifestations of airway remodeling in asthma include airway wall thickening, epithelial cell damage, epithelial reticular basement membrane fibrosis, airway smooth muscle hyperplasia and hypertrophy, mucus gland hypertrophy, and the reconstruction and regeneration of vascular tissues.

Airway wall thickening

The airway wall is thickened in asthmatic patients and can usually be examined by computed tomography (CT). In asthmatic patients, airway wall thickening mainly involves medium- and small-sized bronchi (5–12th levels) (20,21), and the thickening of all airway wall components, including increased airway smooth muscle (ASM) mass, glandular hypertrophy, connective tissue deposition, as well as edema and inflammatory cell infiltration. Notably, airway wall thickness is increased by 50–100% in patients with lethal asthma and 10–100% in patients with non-lethal asthma (22). Additionally, the variability of airway wall thickness has been shown to be correlated with lung function and previous hospitalization, which can indicate the severity of asthma (20).

Epithelial cell damage

Airway epithelial cells form the first physiological barrier of the respiratory tract against external environmental microbes, allergens, and other harmful substances. These cells can identify these substances with pattern recognition receptors and then secrete inflammatory factors, chemokines, and antigenic peptides for intrinsic

and adaptive immune responses, and thus play a crucial role in pulmonary innate immune response. *Ex vivo* and *in vivo* studies have confirmed that airway epithelial cells play a key role in chronic inflammation and airway remodeling in asthmatic airways (23). In asthmatic airway remodeling, structural changes in airway epithelium mainly include epithelial cell shedding, cilium loss, the disruption of adherens and tight junctions, and the interstitial transformation of epithelial cells (24-26). Damaged epithelial cells can be rapidly repaired, and during this process, a variety of growth factors and extracellular matrices (ECMs) are released to promote epithelial cell repair, which also cause the proliferation of fibroblasts, myofibroblasts, and smooth muscle cells and the release of collagen molecules, contributing to airway remodeling. With the shedding of epithelial cells, the airway becomes more sensitive to factors that induce cellular damage; as the adherens junctions and tight junctions among epithelial cells are disrupted, epithelial cell permeability increases and the process of epithelial cell regeneration and repair is prolonged, further contributing to the occurrence of airway remodeling. The phenotypes of epithelial cells differ in the airways of patients with different degrees of asthma (25), suggesting that the severity of asthma may be assessed by detecting changes in epithelial cells and that characteristic changes in epithelial cells may be used as markers for monitoring the progression of asthma.

Thickening of the subepithelial RBM

The thickening of the subepithelial reticular basement membrane (RBM), also known as sub-epithelial fibrosis, is a characteristic change that occurs early in the pathogenesis of asthma, especially in severe asthma (27). Subepithelial RBM thickening occurs due to the deposition of a number of ECM proteins, which are composed mainly of fibronectin, myostatin, and collagen types I, III, and V; however, the levels of laminin and collagen IV are normal. Fibroblasts play an important role in this process (28). The transformation of fibroblasts into myofibroblasts upon the stimulation of chronic airway inflammation leads to accelerated cell proliferation and the synthesis of secretion of ECMs, especially collagen fibers. RBM thickening can be used to distinguish between chronic obstructive pulmonary disease and irreversible asthma (24); however, it is not significantly correlated with age at the onset of symptoms or diagnosis, treatment delay, and drug efficacy (29). Recent studies (4-7) have shown that expressions of follistatin-like 1, activin A, interleukin 33, transforming growth factor β (TGF-β), Smad2/3, and matrix metalloproteinases affect RBM thickening. Additionally, omalizumab inhibits RBM thickening (8), but corticosteroids appear to be less effective in this regard (30).

Hyperplasia or hypertrophy of ASM cells

Bronchial smooth muscle accounts for about 5% of the bronchial wall in healthy individuals but 12% in patients with lethal asthma (22). The proliferation of ASM cells is positively correlated with the severity of asthma. In asthmatic patients, the excessive hyperplasia and hypertrophy of ASM cells directly participate in airway wall thickening. Additionally, the ASM cells switch from a contractile to a synthetic phenotype, synthesizing and secreting cytokines, adhesion molecules, ECM components, and other active mediators to exert immune functions. Finally, the ASM cells activate mast cells, eosinophils, T lymphocytes, and neutrophils to participate in chronic inflammation, resulting in airway remodeling and airway hyperresponsiveness. In recent years, the origin of ASM cells has become a hot research topic. An increased number of ASM cells may result from the proliferation of smooth muscle cells *in situ* in the ASM layer, from the aggregation and differentiation of subepithelial fibroblasts and circulating fibroblasts, or from the migration of bone marrow cluster of differentiation 34+ ($CD34^+$) hematopoietic progenitor cells from the circulation and other parts of the lung into the muscle bundles (31,32).

Mucus gland hypertrophy

In many asthmatic patients, mucus plugs, which are often mixed with inflammatory exudates, are observed in the airway lumen and are difficult to clear by coughing, which is an important feature of chronic asthma and severe refractory asthma. In animal models, increased mucus was found to be associated with goblet cell proliferation and increased mucus glands. The thickening of the airway epithelium, along with goblet cell proliferation, the hyperplasia of subepithelial mucus glands, and a 3-fold increase in mucin secretion, leads to the formation of "mucus plugs", which are involved in airflow obstruction in asthma (33).

Angiogenesis and remodeling

Angiogenesis and vascular remodeling have been found to

be important pathological features of asthma, especially in patients with severe and fatal asthma. Angiogenesis refers to the growth of new blood vessels from existing vessels and an increase in the number of blood vessels, while vascular remodeling refers to changes in the structure and/or function of blood vessels, such as increased vessel diameter and permeability, increased exudation, and abnormal responses to vascular regulatory substances. Vascular regeneration causes the swelling of the airway wall and the reduction of the inner diameter, which aggravate airflow limitation and induce the accumulation of pro-inflammatory and remodeling mediators, thus causing airway remodeling. The degree of alteration in the number of these vessels parallels the severity of asthma (19). Increased bronchial vascularity is closely related to the expressions of angiogenic factors including vascular endothelial growth factor (VEGF), angiopoietin, and hypoxia-inducible factor (34).

Airway remodeling in the pathogenesis of asthma

The role of airway remodeling in the pathogenesis of asthma is not yet fully understood. Studies in molecular biology have revealed that airway remodeling is closely related to airway inflammation, which involves a variety of cytokines, growth factors, inflammatory mediators, and enzymes participating in the chronic inflammation in asthma. For example, VEGF, platelet-derived growth factor, TGF-β, epidermal growth factor, connective tissue growth factor, nerve growth factor, leukotriene, and matrix metalloproteinases (35-37) exert their roles through mitogen-activated protein kinases, phosphatidylinositol-3-Kinase and Protein Kinase B (PI3K/AKT), Janus kinase 2/signal transducer and activator of transcription 3, extracellular signal-related kinase 1/2, MEK/ERK, nuclear factor kappa B (NF-κB), and many other signaling pathways (38).

Airway remodeling is not only a secondary event to inflammation. There are some indications supporting the notion that airway remodeling can occur as a primary event. For example, anti-inflammatory drugs and bronchodilators are ineffective on airway remodeling in asthmatics. Choi *et al.* (9) pointed out effects of human adipose tissue- and bone marrow-derived mesenchymal stem cells (MSCs) on airway inflammation and remodeling in a murine model of chronic asthma. Both MSCs alleviated airway inflammation, but human adipose tissue-derived MSC (hADSC) tended to have a more significant effect. Human bone marrow-derived MSC (hBMSC) treatment reduced Th2-cytokine levels but hADSC treatment did not. Both treatments reduced airway remodeling. In addition, in recent years, our team has been devoted to studying the effect of stem cells on airway remodeling, and has achieved certain results.

Quantitative approaches to assess airway remodeling

The initial approach to assess airway remodeling, both in humans and in animal models, has been the histologic analysis of two-dimensional sections by means of light, fluorescence or electron microscopy (5). In clinical trials and laboratory experiments, we often refer to the thickness of the airway wall as the severity of airway remodeling. However, this method cannot reflect the composition and achieve quantitative approaches. In 2010, a joint task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published limitation of two-dimensional sections. Whole lungs obtained from animal models, but also for studying human biopsies are suggested. Therefore, feasible non-invasive airway remodeling assessment tools with high accuracy and sensitivity are urgently needed. Hopefully, novel *in vivo* imaging techniques will be further advanced to allow monitoring development, growth and inflammation of the airways already at a very early stage in life (5).

Treatment of airway remodeling in asthma

It is generally believed that airway remodeling is difficult to reverse once it occurs. Most medications for asthma are developed to alleviate chronic inflammation, and currently, there are no drugs or other interventions available that can definitely reverse airway remodeling in asthma. Reversing airway remodeling can not only relieve asthma symptoms but also prevent disease progression and improve prognosis. Thus, the treatment of airway remodeling in asthma would be highly valuable.

Glucocorticoid therapy

Chronic airway inflammation is the basis of asthma and an important initiating factor of airway remodeling. Inhibiting the inflammatory response can slow down the occurrence of airway remodeling. Glucocorticoids are the first-line treatment for airway inflammation in asthma. Thus, it has been assumed that glucocorticoids can inhibit airway remodeling. Feng *et al.* (39) showed that glucocorticoids

inhibited airway remodeling in rat models of asthma; however, Vanacker *et al.* (40) concluded that glucocorticoids inhibited but did not reverse the structural changes in airways that had already occurred. In animal studies (41-43), glucocorticoids have been shown to inhibit airway remodeling in concert with calcitriol or β2 agonists. Glucocorticoids stop the process of airway remodeling by inhibiting the metaplasia of goblet cells, the hypertrophy and phenotypic transition of ASM cells, the proliferation of lung fibroblasts, the release of inflammatory mediators, and the thickening of the subepithelial RBM and by repairing the epithelial layer (43-45). However, up to 1/3 of asthma patients are clinically insensitive to glucocorticoid therapy (46) for which airway remodeling may play an important role. Bourdin *et al.* (47) found that a limited steroid response to short-acting glucocorticoids in severe asthma was associated with the thickening of bronchial basement membrane, and that RBM thickness could predict steroid responsiveness below 15%. Bui *et al.* (48) demonstrated that ASM cells were insensitive to the anti-proliferative effects of corticosteroids for which the insulin growth factor-binding protein-1 plays a key role. Lo *et al.* (49) also found that patients with severe asthma had an increased number of circulating fibroblasts, a greater potential for myofibroblast differentiation, and diminished expression of glucocorticoid receptors in fibroblasts, and as a result, the effects of glucocorticoids were lowered in these patients. Molecular changes in TGF-β-mediated lung fibroblast-myofibroblast differentiation also have an effect on glucocorticoid resistance (50). Thus, improving airway remodeling may be a new therapeutic strategy for reversing glucocorticoid resistance in asthma patients.

Anti-IgE therapy

Immunoglobulin E (IgE) antibodies activate mast cells to secrete histamine, cysteinyl leukotrienes, and other inflammatory mediators, thus promoting airway remodeling. Omalizumab, a humanized, monoclonal anti-IgE antibody that binds specifically to circulating IgE molecules, has been introduced into asthma treatment (51). The clinical efficacy and safety profile of omalizumab has been well documented in numerous clinical trials in patients with moderate to severe persistent allergic asthma. Studies (52-54) have shown that omalizumab interrupts the allergic cascade by preventing IgE from binding to mast cells, basophils, and antigen-presenting cells. By doing so, it alleviates inflammatory cell infiltration, decreases bronchial mucosal fibronectin deposition and RBM thickness, and even acts directly on IgE-bound ASM cells, helping to reverse airway remodeling. Pregnancy-associated plasma protein-A and galectin-3 may be useful biomarkers for predicting airway remodeling in patients with severe asthma treated with omalizumab (55,56). However, it has also been suggested that omalizumab may have a limited effect on airway remodeling (57). Thus, larger multicenter clinical trials urgently need to be conducted.

Anti-TNF therapy

Tumor necrosis factor-α (TNF-α) plays key roles in inducing epithelial-mesenchymal transition, fibroblast growth and myofibroblast maturation, ASM cell proliferation, smooth muscle generation, and angiogenesis (58-61), and thereby participates in asthmatic airway remodeling. As an important member of the TNF family, LIGHT is a crucial mediator of airway remodeling (62). Clinical studies have confirmed that etanercept, a TNF-α blocker, is effective in the treatment of asthma, as it reduces goblet cell production and improves lung function and airway hyperresponsiveness (63,64). A recent study suggested that Xiaochuanping powder, a traditional Chinese prescription, reduced airway inflammation and remodeling by reducing TNF-α secretion (65).

Vitamin D therapy

Vitamin D notably reduces exacerbations of severe asthma while improving steroid responsiveness (19). The levels of 1,25-$(OH)_2D_3$, which has been recognized as the most important active metabolite of vitamin D, are inversely correlated with asthma severity, glucocorticoid responsiveness/dosage, and markers of pathogenesis, such as airway remodeling, IgE, and eosinophilia (66). 1,25-$(OH)_2D_3$ effectively reduces ASM cell proliferation and inflammatory mediator secretion by inhibiting NF-κB activation, reducing IL-13, and attenuating the effects of TNF-α and TGF-β (67-69). Thus, vitamin D therapy can slow down airway remodeling in asthma and may be a potential treatment option for this condition. However, few studies have examined its clinical application, and thus further research needs to be conducted.

Bronchial thermoplasty (BT)

BT is a nonpharmacological treatment, and its safety, efficacy,

and durability has been well demonstrated in literature (70-73). BT is a bronchoscopic technique that destroys abnormally increased ASM and alters the structure of the airway wall, thereby alleviating airway remodeling, reducing the frequency of severe asthma attacks, and improving quality of life (19). Pathology has confirmed an important link between ASM atrophy and clinically observed improvements in symptoms, and BT increases the luminal airway volume on the treated side (74). It is widely believed that BT reduces airway resistance by altering ASM, thus changing pulmonary function (75). However, while Langton *et al.* observed no changes after treatment in spirometry and no changes in any oscillometry parameter after BT treatment, they found that the residual volume was reduced (76). A recent study found that the response to BT treatment was associated with serum IgE and eosinophil levels, and that the efficacy of BT in different phenotypes of asthma varies (77). In various asthma phenotypes, BT benefits are achieved through different molecular targets (78).

Others

In recent years, the precise treatment of airway remodeling in asthma has been investigated at the levels of genes, stem cells, and immunity. This research has shed new light on the development of individualized treatment protocols. Studies have shown that micro ribonucleic acid (miRNA)-200a reduces ASM cell proliferation and airway remodeling through the FOXC1-mediated PI3K/AKT signaling pathway, miRNA-192-5p may attenuate airway remodeling and autophagy in asthma by targeting MMP-16 and ATG7, and long non-coding RNA plasmacytoma variant translocation, as a novel regulator of the asthmatic phenotype in human ASM, can slow down airway remodeling (10-12). Human mesenchymal stem cell transplantation can inhibit TGF-β1-induced epithelial-mesenchymal transition, airway goblet cell proliferation, and mucin 5ac expression in animal asthma models, thus effectively preventing airway remodeling (13,14). Additionally, sublingual immunotherapy can also affect airway wall thickness in allergic asthma patients (15).

Prospects

In the past few years, there have been research advances in airway remodeling with the rapid development of experimental techniques (13), especially in the areas of slowing down or reversing airway remodeling. As the above-mentioned studies showed, treating airway remodeling is a promising strategy in preventing the occurrence and progression of asthma. However, research on airway remodeling still faces the a number of difficulties. First, as airway remodeling is a progressive process, it is difficult to obtain physical specimens. Further, there is no standardized basic experiments and technical design methods for establishing animal models of airway remodeling. In clinical settings, airway biopsies for specimen collection in asthma patients is highly risky and challenging. Second, there is a lack of feasible non-invasive airway remodeling assessment tools with high accuracy and sensitivity, no long-term multi-center observational study has been conducted, and longitudinal analyses of the etiology, development, persistence, and progression of airway remodeling have often had poor feasibility. Third, the lack of clinically feasible biomarkers for airway remodeling limits clinical research. Fourth, there is no effective drug to reverse asthmatic airway remodeling, and invasive anti-airway remodeling measures are difficult to apply in human subjects. Thus, the research priorities in the near future should include: (I) establishing animal models of airway remodeling; (II) reaching consensuses on the definition and measures of airway remodeling and establishing scientific platforms for exploring the etiology, pathogenesis, and persistence of airway remodeling; (III) identifying the early biomarkers of airway remodeling and using genetic and phenotypic markers to identify high-risk groups; and (IV) actively developing drugs for controlling airway remodeling based on the mechanisms that exacerbate airway remodeling, and applying more interventions from the perspectives of genes and stem cells. Breakthroughs in these areas will open up new avenues in the research and treatment of asthma (17).

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2835/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.

amegroups.com/article/view/10.21037/atm-22-2835/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 The search strategy of PubMed

Items	Content
Search url	https://pubmed.ncbi.nlm.nih.gov/advanced/
Add terms to the query box	((Asthma[MeSH Terms]) AND (airway remodeling)) AND (pathological features) , ((Asthma[MeSH Terms]) AND (airway remodeling)) AND (treatment), *et al.*
Text availability	Abstract and Full text
Article attribute	Associated data
Article type	Books and Documents, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review
Publication date	2001-03 to 2022-07

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