



# Status and prospects: personalized treatment and biomarker for airway remodeling in asthma

Jintao Zhang, Liang Dong

Department of Respiratory and Critical Care Medicine, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

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*Correspondence to:* Liang Dong. Department of Respiratory and Critical Care Medicine, Qilu Hospital, Cheeloo College of Medicine, Shandong University, 107 Wenhuxi Road, Jinan, China. Email: dl5506@126.com.

**Abstract:** Airway remodeling, as a major characteristic of bronchial asthma, is critical to the progression of this disease, whereas it is of less importance in clinical management. Complying with the current stepwise treatment standard for asthma, the choice of intervention on the clinical status is primarily determined by the patient's treatment response to airway inflammation. However, a considerable number of asthmatic patients, especially severe asthmatic subjects, remain uncontrolled though they have undergone fortified anti-inflammation treatment. In the past few years, a growing number of biologics specific to asthma phenotypes have emerged, bringing new hope for patients with refractory asthma and severe asthma. While at the same time, the effect of airway remodeling on asthma treatment has become progressively prominent. In the era of personalized treatment, it has become one of the development directions for asthma treatment to find reliable airway remodeling biomarkers to assist in asthma phenotypes classification, and to further combine multiple phenotypes to accurately treat patients. In the present study, the research status of airway remodeling in asthma is reviewed to show the basis for classifying and treating such disease. Besides, several selected airway remodeling biomarkers and possibility to use them in individual treatment are discussed as well. This study considers that continuously optimized mechanisms and emerging biomarkers for airway remodeling in the future may further support individual therapy for asthma patients.

**Keywords:** Asthma; airway remodeling; biomarker; personalized treatment

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## Introduction

Asthma, as a highly prevalent respiratory disorder worldwide, refers to a chronic noncommunicable airway disease primarily manifested by airway inflammation, airway remodeling, as well as airway hyperresponsiveness. Recently, asthma has become progressively prevalent and currently affected about 334 million people worldwide (1). As suggested from the latest GINA (2), bronchial asthma is defined as a heterogeneous syndrome instead of a single disease. It exhibits varying symptoms and intensity over time with variable expiratory flow limitations. Note that for

asthmatics exhibiting similar clinical manifestations, they may develop highly different endotypes and phenotypes, thereby adversely affecting their responses to treatment (3). Given the complexity of airway remodeling, existing studies on asthma phenotypes placed a major emphasis on airway inflammation (4).

Acting as a main feature of asthma, airway remodeling is critical to determine progression of the disease. Early detection aided by effective intervention to airway remodeling may down-regulate the incidence of acute asthma attacks and mitigate severe damage (5,6). As fueled by the recent advancement of different assistive

technologies, the outline of airway remodeling is emerging step by step. Under the background of personalized therapy, seeking effective biomarkers for airway remodeling classification and precise treatment of asthmatic subjects has become one of the future development directions for asthma treatment.

In this paper, we review the published literature on some of the potential biomarkers and therapy aiming at airway remodeling in asthma. The current status and encountered problems of airway remodeling research are also highlighted, in order to explore the possibility for personalized treatment of asthma based on airway remodeling.

## Research status of airway remodeling in asthma

### *Characteristics of airway remodeling in asthma*

Asthmatic airway remodeling was initially proposed in 1922 (7). Numerous studies on airway remodeling have been conducted or are ongoing. Multiple asthma studies based on human subjects have been conducted in depth, underpinning further expansion and clinical applications. Airway remodeling covers multiple cell interactions (8), which is primarily characterized by airway epithelial variations, reticular basement membrane (RBM) thickening, mucous glands hypertrophy, smooth muscle hyperplasia/hypertrophy as well as angiogenesis. All of these variations in airway components interact with each other, eventually leading to adverse outcomes (e.g., airway wall thickening, epithelial dysfunction, and abnormal mucus secretion) (9). Compared with healthy subjects, the thickness of airways in asthmatic patients could increase significantly. Studies suggested that airway wall thickness in patients with fatal asthma increased by 50–300%, and that of non-fatal asthma patients increased by 10–100% (10). Furthermore, the obstruction will be exacerbated by excessive mucus secretion and inflammatory hyperemia (11).

Studies reported airway remodeling existing in the early stages of asthma patients even before clinical manifestations (12). It was not just related to the progressive response to long-term persistent inflammation that was initially considered. It is noteworthy that even without other inflammations, mechanical stresses caused by bronchoconstriction may also induce airway remodeling (13,14).

### *Significance of airway remodeling research in asthma*

Previous studies reported that respiratory and airway

function is not completely parallel to airway inflammation and may be related to airway remodeling (15). Similarly, other researchers considered that though there are overlapping links between airway inflammation and remodeling, the two should still pertain to different systems (16). Each of them has its own set of pathogenesis and affects each other over asthma development. Studies combining the analysis of inflammation and airway remodeling can provide more insights into the complete pathophysiology of asthma (17).

Besides overlapping with inflammatory mechanisms, airway remodeling is also related to airway hyperreactivity, whose persistence and exacerbation are partially attributed to some airway remodeling events (e.g., collagen deposition and increased airway smooth muscle mass and contractility) (18).

Remodeling can change airway structure and may gradually lead to fixed airway obstruction. For asthmatics, fixed airflow limitation may not act as a curable trait, whereas it is a feature that should be treated correctly to prevent overtreatment (19). Moreover, it has also been considered one of the vital features of numerous severe asthmatics (20). For health-care expenditure, though severe asthma only accounts for a small proportion of the asthma population, it assumes the majority of the medical expenses and social pressure while airway remodeling acts as a prominent trait for severe asthmatics (21,22).

For children with asthma, multiple birth cohort studies reported that airway structural variations can take place in early childhood in parallel with permanent lung function damage, and that the reticulum basement membrane is considered a predictor of future asthma development, independent of airway smooth muscle thickness or eosinophilic inflammation (23). On the whole, airway remodeling is an imperative problem that should be faced and resolved.

### *Research dilemmas in airway remodeling*

The complexity of airway remodeling is reflected by its involvements in different tissues and cell types, as well as its interrelationship with a range of biological processes. Its slow progress is mostly caused by many unknown factors of pathophysiological mechanisms and difficulties in clinical application (24).

As the most commonly used existing disease model, mice models are extensively used in asthma research (25), whereas it has many restrictions. First, mice cannot develop asthma naturally, and only some specific types of asthma can be

induced artificially in mice. Second, mice are significantly different from humans in airway structure and size (26,27). Both of them have highly impacted the asthma research, especially for airway remodeling.

Biopsy is generally known as the most effective method to assess the extent of airway remodeling in asthma patients. Moreover, imaging examinations, especially CT, are also considered a useful way to assess airway remodeling in human asthma subjects. However, all of these techniques are limited by practicality and ethicality (28).

Moreover, the airway remodeling we have often observed and measured is confined to large and medium-sized airways for the finite of technical level. However undoubtedly, bronchioles and other smaller bronchus can also participate in this progression. Airway remodeling may have different effects on the smaller ones (29) for their distinct components and structures. However, it is difficult to investigate airway remodeling.

Besides, existing studies on asthma were primarily conducted using cross-sectional methods (30), whereas the prominent feature of airway remodeling is that it is a longitudinal process involved long-term evolution, which also adds obstacles to airway remodeling research.

### ***Basic research for airway remodeling***

Though airway remodeling has several adverse effects as mentioned on human subjects, causing decreased lung function and persistent and progressive airflow limitation, it indeed has some benefits. For asthma patients, airway remodeling could inhibit airway contraction and counteract excessive narrowing (18,31). Thus far, the complete mechanism of airway remodeling remains unclear, and it is unwise to blindly intervene airway remodeling. How to prevent the pathological airway remodeling effectively and return it to the track of reasonable repair smoothly now is the lead object of existing asthma studies. Similar to many existing effective approaches to manage diseases, successful management of asthma is also determined by the insights into its basic biological processes and dysfunction in the context of disease (32).

Over the past few decades, airway ecological characteristics of asthmatics have been further explored (33), and different mechanisms and cellular interactions in asthma have been extensively delved into (e.g., autophagy and senescence) (34,35). As the basic research has been deepening, the whole framework of remodeling mechanisms in asthma continues to be perfect.

Epidemiological studies reported that both genetic and environmental factors can reduce lung function and increase the likelihood of airway remodeling (36). In the field of asthma-associated gene, genetic researches related to airway remodeling have been rarely conducted. Though over 100 genes have already been proved related to asthma, only few of them are linked to decreased lung function of asthma (37). It has been demonstrated that three genes variants, namely, *IL-13*, *PLAUR* and *CHI3L1* (38-40), are associated with airway remodeling in asthma.

Among various asthma animal models, equine asthma models have also aroused more attention from zoologists in recent years. Compared with mice, horses can spontaneously produce asthma, while its larger respiratory system is also easy to observe and research for airway remodeling. Besides, isolating inflammation and airway remodeling may be even likely to take place in asthma equine models (17), making equine model an appropriate model to study non-eosinophilic asthma.

Considerable puzzles remain in airway remodeling, and more intensive basic studies are still required to demonstrate whether these experiments are performed longitudinally or horizontally. These are necessary to provide more insights into the entire process and subsequently the choice for treatment methods.

### ***Advanced assistive technologies for airway remodeling***

In the past, for the complexity of airway remodeling involving the chain reaction of multiple cellular molecules at different periods and the limitations of multiple detection technologies, it has always been difficult to explore it. Even biopsy is a reliable method for diagnosis of airway remodeling, as an invasive detection technique, its function is limited. Now optimized assistive technologies, including advances in imaging technology and measurement indicators (41-43), can be adopted as a feasible way to delve into and exploit this character.

Spirometry is currently the gold standard for the diagnosis of asthma, but it is short in intuitively reflecting structural airway changes (44). CT is an important technology to diagnose multiple respiratory diseases; it is also conducive to measuring the degree of airway remodeling. In previous studies, fractional exhaled nitric oxide (FeNO), as one of the non-injury markers reflecting chronic inflammation in asthma patients, was considered unrelated to the airway thickness in asthma patients (45). After accurate sub-generation of bronchial trees, a three-

dimensional CT analysis was conducted by researchers (46), and the results indicated that FeNO in asthma patients was associated with thickening of bronchial walls in the third to the sixth generation. It is therefore suggested that FeNO might be useful in assessing airway structure variations in asthma patients, especially in the distal airway. Moreover, some researchers conducted high-resolution CT studies and demonstrated that airway remodeling in asthma was more significant in the distal airway and subbronchial lobes; thus, it was reported that airway remodeling could help predict small airway involvement and identify targets for local treatment of asthma, as well as serve as a predictor of early asthma (47,48). Another report (49) also proposed a novel concept for assessing airway in CT. It was revealed that in quantitative CT (qCT), calculating the percentage of tracheal cavity area, Delta Lumen, could indicate adverse outcomes and airway remodeling in asthma patients. With the development of CT, more insights into airway remodeling have been gained.

Apart from CT, there are many other assistive technologies assisting in evaluating airway remodeling. Adams *et al.* (50) used a birefringent fiber platform to observe airway smooth muscle *in vivo*. Meantime, they improved the imaging ability to observe the structure and function of airway smooth muscle in asthma patients. Replacing the conventional tissue staining method by high-resolution nonlinear optical microscopy (NLOM), researchers tested the lungs of asthmatic patients and control and reported that the levels of disordered and broken fibrous collagen in the airway remodeling extracellular matrix (ECM) of asthmatic patients were elevated, further enriching the relevant characteristics of airway remodeling (42).

Since airway remodeling can change the respiratory tract not only in quantity but in property (51), airway remodeling is still being roughly measured even under the support of multiple technologies. However, it cannot be disclaimed that following the introduction of novel parameter and progress of technologies, obstacles ahead are being continuously reduced.

### **Airway remodeling biomarkers in asthma**

The proper classification of asthma by biomarkers or any other means is the premise of individualized treatment. In recent years, biomarkers have aroused increasing attention in the diagnosis and control of diseases, including diabetes and cancer (52). It is currently known that asthma-related

biomarkers can be obtained in various sources (e.g., urine, blood, bronchoalveolar lavage fluid, induced sputum, exhaled gas agglutination, and bronchial biopsy). For minimal invasion and reproducibility, blood and exhaled breath may show more advantages over others (41,53). In asthma, especially severe asthma, several biomarkers already available for clinical practice including blood eosinophil, sputum eosinophil and neutrophil, serum total IgE and FeNO, which could reflect underlying airway inflammation (53).

### **Significance of airway remodeling markers**

Though considerable efforts have been paid to verify the importance of airway remodeling in asthma, the lack of accessible and valid biomarkers for clinical application has also become a major problem hindering the progress of airway remodeling research (17), the emphasis of most biomarkers is still placed on the inflammatory response in this disease. As one of the causes of chronic irreversible damage in asthma, airway remodeling exerts extensive and far-reaching impact on asthma patients.

For low T2 asthma, it was reported that patients with T2 low asthma usually lack a history of environmental allergies and less responsive to corticosteroids (54). For the absence of effective biomarkers, exclusion methods have been generally used to support diagnosis of low T2 asthma (55). In this case, biomarkers reflecting airway remodeling may be conducive to identifying this phenotype.

### **Exploration of airway remodeling marker in asthma**

The current overlaps of biomarkers reveal that distinguishing asthma phenotype may require not one but a group of biomarkers (56) to accurately classify the endotype of asthma. Many proteins and cytokines have been confirmed to be associated with airway remodeling in asthma (e.g., periostein), which has been extensively studied in recent years (8). It is inevitable that their remodeling function mostly overlaps with inflammation. Besides, for many limitations, the level of airway remodeling in human-based studies is usually reflected in the response to treatment (e.g., improvement in lung function and FEV1) (57-59). Though researchers have confirmed the correlation between the variations in lung function and airway remodeling (60), these variations are indirect and ambiguous. It is difficult to effectively analyze and estimate the level of remodeling via these methods, while patients' remodeling phenotypes are more difficult to classify.

Furthermore, some scholars considered that imaging technologies can also act as markers of airway remodeling, including the application of qCT and ultra-polarized nuclear magnetic resonance imaging (60). Researchers can even use imaging methods to classify asthma patients and guide further treatment (61). However, imaging technologies are so roughly to observe and calculate the airway structure and cannot accurately distinguish airway hierarchy. More importantly, their applications in asthma are also confined by practicality and economy.

### *Potential airway remodeling biomarker*

Multiple Studies based on bronchoalveolar lavage and endobronchial biopsies have proposed plenty of feasible biomarkers (e.g., matrix metalloproteinase-9, protease-activated receptor 2 and even its ligands (62-64) that are related to airway remodeling). However, most of the mentioned molecules should be collected from biopsy or alveolar lavage fluid, which is invasive and labor-intensive (65), thereby limiting their clinical applications. Unlike others, there are three potential molecules, namely, galectin-3 (Gal-3), YKL40, and VitD. It has been proven by biopsy that these molecules in blood can partially reveal the change of airway structure, revealing that they may be practically used to support the diagnosis of airway remodeling.

#### **Gal-3**

Gal-3 that can be secreted and measured in the blood is a shared factor in fibrosis formation in different organs (66). Thus, it has been considered a biomarker, associated with many diseases (e.g., heart failure) (67). In animal model, the Gal-3 knockout mice have been successfully established. Following experiments validated that Gal-3 could promote airway remodeling via secretion of multiple cytokines as well as recruitment of inflammatory cells (68). After analyzing the RBM thickness, eosinophil and neutrophil infiltration, and proteomics characteristics of eight severe asthmatic patients via bronchoscopy biopsies, researchers reported that Gal-3 as a biomarker could effectively reflect the reduction of bronchial smooth muscle (BSM), eosinophilic inflammation and muscle protein component in asthmatics (69,70). However, for the small sample size, the results have many limitations, which require further experimental verification. Additionally, as a pro-fibrotic molecule Gal-3 is also a biomarker of heart disease and fibrosis. The level of Gal-3 in serum may correlate with inflammation and other fibrosis processes as well, independent of remodeling in asthma (71).

#### **YKL-40**

As a member of the mammalian chitinase-like protein family, YKL-40 refers to an inflammatory glycoprotein whose exact function remains unclear (72). Now, it is considered involved in many pathophysiological processes (e.g., inflammation, injury and tissue remodeling) (73). Previous research confirmed that CHI3L1, the gene encoding YKL-40 protein, was associated with airway remodeling in asthma (38). Bara *et al.* (74) conducted studies on airway biopsy samples from 40 asthmatic patients and reported the close relationship between YKL-40 and airway remodeling. The results showed that YKL-40 can promote BSM cell proliferation and migration by PAR-2-dependent pathway. In addition, the expression of YKL-40 in epithelial was positively associated with BSM mass in asthma. In serum sample, Konradsen *et al.* (75) compared serum YKL-40 levels in children with therapy-resistant asthma (n=34), controlled persistent asthma (n=36) and healthy control (n=27). In children with therapy-resistant asthma serum YKL-40 levels were at the relatively high level and closely related to airway thickness and asthma control. Above all, through biochemical and immunohistochemical analysis, Chupp *et al.* (76) found that YKL-40 levels in serum were correlated with the thickness of airway subepithelial basement membrane. Similar to Gal-3, YKL-40 also increased in other fibrotic diseases like idiopathic pulmonary fibrosis (77).

#### **VitD**

Within the last few years, vitamin D has aroused huge attention from the scientific communities (78). A number of respiratory diseases, including asthma have now are related to vitamin D deficiency. Retrospective studies have shown that some trials support the beneficial role of vitamin D supplements in reducing the severity of asthma in children (79). It was speculated that vitamin D may improve airway inflammation and remodeling of asthma through multiple immune pathways including inhibition of growth of BSM cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1 (80). Studies (81) suggested that children with treatment-resistant severe asthma have significantly lower serum 25(OH)D<sub>3</sub>, the main circulating form of vitamin D, than children with mild to moderate asthma. In the subsequent study, researchers collected airway biopsies and confirmed that lower 25(OH)D<sub>3</sub> levels in patients' serum were associated with increased airway smooth muscle mass, poor lung function as well as asthma control. Furthermore, 25(OH)D<sub>3</sub> levels were even unrelated

to any other parameters of airway remodeling (e.g., airway inflammation). Despite its advantages, 25(OH)D<sub>3</sub> also has many disadvantages. Previous studies have found that serum 25(OH)D<sub>3</sub> levels may be affected by gender, age, season and several chronic disease (82,83).

Given considerable restrictions, most studies on airway remodeling biomarkers in asthma have been limited to small samples. For airway remodeling, the variations of airway structure, some results derived from sputum other than serum may be more convincing, whereas the relative studies have been rarely conducted. At all events, more studies are still required for further demonstration.

### Asthma treatment and airway remodeling

Though the phenotype and endotype of asthma have aroused increasing attention, anti-inflammatory treatment remains the pillar of asthma treatment. The association between existing treatment methods and endotype or phenotype remains insignificant in asthma. Anti-inflammatory therapy for asthma has been gradually standardized and improved on clinical practice, while airway remodeling is considered the least affected by current pharmacological and biological treatments (24). Such significant gap provides the more possibility for future development.

#### *Effects of present treatment methods on airway remodeling*

##### **Glucocorticoid**

Glucocorticoid was demonstrated as the major drugs in current asthma therapy that can obviously ameliorate inflammation, whereas its impact on preventing or reversing airway remodeling remains under discussion. One study enrolled 45 corticosteroid-naïve patients with persistent asthma and 28 healthy controls and conducted helical computed tomography. Their results reported that glucocorticoid can partially enhance lung function and decrease the thickness of the airway in asthma patients (84). However, many other opinions suggest that glucocorticoid cannot or slightly impact airway remodeling (85,86), probably because of their different research object, drug dose, administration period and the size of the sample. However, to make matters worse, several studies revealed that inhaled glucocorticoids might have deleterious effects on airway epithelium (e.g., inducing apoptosis and impairing epithelial migration), thereby inhibiting its therapeutic effect for considerable aspects of asthma (87).

##### **Monoclonal antibodies**

A wealth of clinical trials regarding monoclonal antibodies suggested that a variety of IL-5 monoclonal antibodies (e.g., mepolizumab and reslizumab) can facilitate airway remodeling in asthma, including reducing the expression of ECM protein in the RBM, thereby partially restricting airway remodeling (48). For patients with long-term asthma with persistent airway obstruction, however, the current biologics have limited effects (28,88-90). Though large-scale clinical trials have suggested that the new monoclonal antibodies against IL-4/IL-13, [e.g., dupilumab and tralokinumab (91,92)] can effectively reduce the onset of asthma and improve FEV<sub>1</sub>, their exact effects on airway remodeling require further research. Studies (93) showed that IL-33 can increase RBM thickness in children with severe therapy resistant asthma (STRA) which was proven by endobronchial biopsies. After steroid treatment, IL-33 alone appears to be sufficient to sustain remodeling in the absence of IL-13. In general, IL-33 may act as a direct target for asthma treatment in the future due to its impact on reducing airway remodeling in STRA.

##### **Bronchial thermoplasty**

Bronchial thermoplasty brings emerging hope to treat airway remodeling in asthmatics. As a novel non-drug intervention, bronchial thermoplasty can impact the airway through thermal energy. Such technique significantly improves the patient's symptoms and quality of life (94) primarily by reducing excess airway smooth muscle, which has achieved promising results in clinical practice (95). It has proved that BT has slight variations in airway epithelial, mucinous gland and goblet cell hypertrophy or hyperplasia (96). However interestingly, some studies reported that the reduction of airway smooth muscle alone is not sufficient to explain its clinical results; they also consider that the reduction of airway smooth muscle mass cannot be completely caused by direct acute heating (97). For this novel technology, its mechanism of action to reduce the incidence of adverse reactions and improve patient outcomes requires further investigation.

Furthermore, other drugs [e.g., LAMA and LABA (98,99)] have also been shown to improve airway remodeling, whereas they have also only been performed in animal models of asthma. Besides, there have been no data assessing outcomes of airway remodeling in asthmatics treated with these drugs.

Though the exact effect of current asthma treatment

methods on airway remodeling requires further studies, it is undeniable that for multiple chronic airway diseases including asthma (67), more advanced and appropriate treatments are imperative to satisfy the requirement for this permanent airway injury.

### *Prospect of airway remodeling therapy*

#### **Calcium receptor antagonist**

Gallopamil, a calcium receptor antagonist, has been demonstrated *in vitro* experiments to be able to inhibit airway smooth muscle cell proliferation (100,101). A 12-month double-blind controlled clinical trial was conducted (100), and the results proved that gallopamil could reduce the thickness of airway smooth muscle in patients with severe asthma without affecting the inflammation. As a result, the acute attack of asthma could be reduced, and the treatment of airway remodeling can be more effectively achieved.

#### **Antihistamine**

Released from mast cells, histamine has been thought to play an important role in the pathogenesis of allergic asthma (102). Previous research has shown conflicting results as to whether antihistamines are good or bad for asthma (103). Kunzmann *et al.* (104) reported that histamine can induce the expression of connective tissue growth factor CTGF in cultured lung fibroblasts and up-regulate the occurrence of chronic airway remodeling. Meantime, studies experimentally proved that (105) antihistamines exerted significant relief effect on asthma control and could enhance lung function. Accordingly, a theoretical possibility is provided for the use of antihistamines in asthma to some extent.

#### **Leukotriene receptor antagonist**

Given orally, montelukast is the most clinically-used leukotriene receptor antagonist in treating asthma. It has been proven that Montelukast ameliorated symptoms, rescue medication use and pulmonary function, and reduced the rate of exacerbation in asthmatics (106). For airway remodeling, limited evidence demonstrated the effectiveness of leukotriene inhibitors for the treatment or prevention of airway remodeling (107). Montelukast was also found to be able to inhibit the function of airway fibroblasts in mild asthma patients (108), and it might act as an effective method to facilitate airway remodeling and mitigate airway inflammation.

#### **Prostaglandin D type 2 (PGD2) receptor antagonist**

Existed evidence verified that PGD<sub>2</sub>, which acts on the PGD<sub>2</sub> receptor 2 (DP<sub>2</sub>) have an important role in mediating eosinophilic airway inflammation in asthma and might be a promising target for the treatment of asthma (109). In a randomized placebo-controlled trial, researchers reported, as DP<sub>2</sub> antagonist, fevipiprant could induced airway smooth muscle mass in bronchial biopsies from asthmatics (110). They also confirmed suppressed airway smooth muscle migration via using DP<sub>2</sub>-specific antagonists in an airway smooth muscle cell culture model (110). However, fevipiprant failed to improve lung function effectively in phase 3 trial.

### **Possibility of personalized therapy for airway remodeling**

For many years, asthma treatment was primarily based on a “one treatment fits all” principle and the disease situation is not under control especially in some severe subjects (55). In the era of individualized therapy, treatment strategy according to different phenotypes of asthma can maximize the control of diseases. Gaining the insights into the degree and classification of airway remodeling may contribute to prevention and treatment of asthma.

As mentioned above, after years of research, the current research on airway remodeling has made significant progress, but having some distance from the practical application. Individualized treatment considers the patient as a whole and takes many factors including the patient's psychology, economy and other aspects into account not just the disease and the corresponding pathological mechanism (111). However, the complete mechanism of asthma especially airway remodeling has not been elucidated, which is the first step. Our understanding of the mechanism of airway remodeling in asthma is still in its infancy and remains to develop.

Different patients have unique remodeling phenotypes, which to some extent makes them respond to drugs differently, and their distinct phenotypes should be identified and precisely assessed for individualized treatment (8). Finding several reliable characteristics or biomarkers that can accurately distinguish phenotypes of patients lays the foundation for applying individualized treatment practically. Recently, researchers (112) developed a novel classification method for asthma which based on topological data analysis. They perform multidimensional data analysis to incorporate multiple features of airway remodeling, and successfully

split asthma patients into four pathotypes. This analysis method further enriches the contents of each phenotype of asthma. At present, in the absence of effective airway remodeling biomarkers, such unusual method classifies the phenotype of asthma across the board and makes it possible for the next step of individual treatment.

Therapeutically, the improvement is made from having only one monoclonal antibody to a set of biologics with various targets and functions, and we will have to select some of them to make the right clinical decision (113). This further emphasizes the significance of searching for effective biomarkers and further reasonably performing asthma phenotyping to ascertain the correct treatment for the respective patient.

## Conclusions

Thus far, there are still lots of puzzles in research about airway remodeling. Identification of ideal airway remodeling biomarkers in asthma remains inconclusive not to mention utilization. With the emerging of increasing biologics, compared with finding some novel and reliable biomarkers, further exploring the complete mechanism of airway remodeling is still in the first place. During the period of the progressively improvement on pathophysiologic mechanisms, suitable airway remodeling markers will gradually appear. When achieving asthma control, precise classification based on the biomarkers or other methods should be achieved. On that basis, an ideal equilibrium state can be finally achieved.

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## Footnote

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*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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