Airway remodeling: a potential therapeutic target in asthma

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Background: **Apart from airway inflammation, airway remodeling is one of the main pathological features of asthma. However, it remains unclear when airway remodeling starts in children and whether it could be a potential therapeutic target in asthma.**

Data sources: **We have reviewed the recent literature regarding structural changes after airway remodeling, the relationship between airway inflammation and airway remodeling, the relationship between childhood asthma and airway remodeling, and the role of long-term medication in asthma treatment for airway remodeling.**

Results: **The relationship between airway inflammation and airway remodeling is still controversial. A number of morphological and pathological studies have confirmed that airway remodeling occurs not only in adult asthma, but also in childhood asthma. It develops early in the disease process of asthma. At present, long-term medication in asthma treatment mainly focuses on anti-inflammation. However, there are no therapeutic interventions that revert airway remodeling once it is established.**

Conclusions: **Airway remodeling may provide a possible new therapeutic target in the management of asthma. It is imperative to strengthen the research in developing new medications specifically for asthma airway remodeling. Prevention and treatment of airway remodeling become top priority in future asthma research.**

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Introduction

Asthma is a major cause of chronic morbidity and mortality throughout the world. There is evidence that the prevalence of asthma has increased considerably over the past 20 years, especially in children. Airway inflammation and airway remodeling are two main pathological features of asthma. It is a consensus that asthma is a non-specific airway inflammatory disease. Many cells such as eosinophils, T-lymphocytes, neutrophils, mast cells, epithelial cells and cellular components are involved in asthma airway inflammation. Although it is recognized as an important pathological process of asthma, at present time, long-term management of asthma still emphasizes control of airway inflammation. In this article, we will discuss the change of airway structures after airway remodeling, the relationship between airway inflammation and airway remodeling, the relationship between childhood asthma and airway remodeling, and the role of long-term medical therapy in asthma management. We believe that airway remodeling may become a potential therapeutic target for the treatment of asthma.

Structural changes after airway remodeling

The structures of normal trachea and bronchial tissue are composed of mucosa, submucosa and adventitia. Mucosal epithelium is pseudo-stratified ciliated columnar, where goblet cells are scattered. A single row of basal cells can be visualized in mucosa basement membrane. Mucosal lamina contains elastic fibers, lymphoid tissue and plasma cells. Submucosa is a layer of loose connective tissue. Adventitia is formed by hyaline cartilage and loose connective tissue.

Huber and Koessler[1] first brought up the concept of airway remodeling in 1922. The paper provided a comprehensive perspective of the histopathological features of asthma that remains relevant today. In the study, 21 patients having fatal asthma were found with severe stenosis of airway lumen, mucosal hypertrophy, airway wall thickness and inflammatory cell infiltration. A number of morphological and pathological studies further confirm airway structural changes such as airway wall thickness, subepithelial fibrosis, airway lumen stenosis, mucous gland hyperplasia, hyperplasia

and hypertrophy of myofibroblasts, muscle cells, and epithelial cells. These changes were found not only in severe asthma, but also in mild cases.[2-9] In addition to inflammatory cells such as eosinophils, activated T cells, mast cells and macrophages, structural tissue cells, which include epithelial cells, smooth muscle cells and fibroblasts, can also play important roles in the pathogenesis of asthma through the release of a number of cytokines, chemokines and mediators. This results in an acute inflammatory response characterized by vascular leakage, epithelial shedding, mucus hypersecretion and widespread airway narrowing. At the same time, the infiltrated epithelial and mesenchymal cells can induce airway structural changes, such as increased thickness of the basement membrane, increased collagen deposition, changes in bronchial microcirculation, and smooth muscle hypertrophy and hyperplasia.[10] Until recently the definition of airway remodeling has been mainly based on a histological description including airway wall thickening, collagen deposition, matrix deposition, smooth muscle hyperplasia and hypertrophy, myofibroblast proliferation and mucus metaplasia, epithelial goblet cell metaplasia and hyperplasia, subepithelial fibrosis, and subepithelial reticular layer thickening.[11,12]

The relationship between airway inflammation and airway remodeling

The relationship between airway inflammation and airway remodeling is still controversial. There are two different opinions about it.

Some scholars think that airway remodeling is the consequence of airway inflammation. Airway remodeling consists of the structural changes that may occur in asthmatic airways in response to persistent inflammation.[13] Tanaka et al[14] found that in the murine model, airway eosinophilic inflammation was responsible for the development of airway remodeling in allergic bronchial asthma. Airway inflammation is a characteristic feature of bronchial asthma. Currently, the prevailing hypothesis is that the Th2 subgroup of $CD4^+$ lymphocytes orchestrate the inflammatory response in asthma. Chronic Th2 inflammation may result in airway remodeling.[15] Airway inflammation and airway structure in asthma interact through the epithelium and underlying mesenchyma. As in other chronic inflammatory disorders, a dynamic interaction between cytokines, growth factors and mediators provides a broader base to identify novel preventative and therapeutic strategies in asthma.[16] It is possibly that several immune and inflammatory cell types and mediators are involved in mediating airway remodeling. Several important candidate mediators of airway remodeling have been identified, including TGF-beta and Th2 cytokines (including IL-5 and IL-13), as well as vascular endothelial growth factors, metalloproteinase 33, matrix metalloproteinase 9 and disintegrin. Airway remodeling mouse models have provided important insight into potential mechanisms by which TGF-beta activation of the Smad-2/3 signaling pathway may contribute to airway remodeling. Human studies have proved that anti-IL-5 reduces levels of airway eosinophils expressing TGF-beta as well as levels of airway remodeling as assessed in bronchial biopsies. Further studies demonstrating these observations and alternate studies targeting additional individual cell types, cytokines and mediators are needed in patients with asthma to determine the role of candidate mediators of airway inflammation on the development and progression of airway remodeling.[17]

However, other studies proposed that airway inflammation and airway remodeling are parallel processes, triggered by the same underlying problem, but the progression of each is independent.[18] The remodeling process itself may be independent of airway inflammation, may be a primary event in the natural history of asthma, and may contribute to the development and persistence of the airway inflammatory process itself.[19] Pohunek et al[20] found there were no links between the number of EG2-positive cells, which was one of the landmarks of eosinophil activation, or the thickness of the subepithelial collagen layer and the duration of symptoms, or the age of the patients, suggesting that paralleling with long-term inflammation such pathognomonic changes occurred early. Furthermore, Fedorov's finding[11] was consistent with four reports[2,21-23] showing no requirement for eosinophilic inflammation that leads to the thickness of subepithelial reticular basement membrane. This suggests a dissociation between airway inflammation and airway remodeling at least in some asthmatic children, although we could not completely exclude the possibility of previous eosinophilic inflammation in these asthmatic children.

Airway remodeling in childhood asthma

The existence of the pathological features of airway remodeling in adult asthma has been confirmed, but the existence of airway remodeling in childhood asthma is still controversial. Airway remodeling used to be considered as a secondary phenomenon which developed late in the disease process as a consequence of persistent inflammation and did not exist in childhood asthma.

However, some findings proved that such pathological features of airway remodeling occurred in some asthmatic children. Remodeling of the small airways developed early in asthmatic children whose airways were undergoing rapid growth and were persistent throughout life.[24] The thickening of reticular basement membrane (RBM) is pathognomonic of the asthma process. Payne et al[2] found that RBM thickness in asthmatic children was similar to that in adults with either mild or life-threatening asthma and greater than that in non-asthmatic controls. Similar to the findings in adult asthma patients, the thickening of RBM was present in children with severe asthma. Kim et al[25] also found basement membrane thickening in children with asthma. Cokugras et al[21] studied 10 moderate asthmatic children with a mean disease duration of 4.8 years, who were treated with sodium cromoglycate for 2.0 years and had received inhaled steroids and bronchodilators for 8 months. Bronchial biopsy specimens were observed with light or electron microscopes. The most important finding was the thickness and hyalinization of the basement membrane in 9 out of 10 patients. Overactive fibroblasts were also present. Eosinophils were seen in one biopsy sample. To better characterize the disease process, Jenkins et al[22] performed bronchoscopy with endobronchial biopsy in six children with difficult-to-control asthma. In each child, endobronchial biopsies showed the change which was consistent with airway remodeling, i.e., increased thickness of the basement membrane, smooth-muscle hypertrophy with varying degrees of goblet cells and hyperplasia of submucous glands. Tillie-Leblond et al[26] also found that severe asthmatic children presented structural abnormalities representing airway remodeling. Using histochemistry and immunohistochemistry, Barbato et al[3] quantified basement membrane thickness, epithelial loss, the number of vessels and inflammatory cells in the subepithelium of asthmatic children. They found that basement membrane thickness and epithelial loss were increased in children with asthma when compared with controls and atopic children. Basement membrane thickness and epithelial damage, which are pathologic features of adult asthma, were present even in those children with asthma. Therefore, it is considered that airway remodeling plays an important role in asthmatic children. In children with steroid-dependent asthma, those with moderate to severe asthma, and those with difficult-to-control asthma, their pathological features are airway remodeling rather than eosinophil infiltration.

Pohunek et al[20] examined bronchial biopsy samples from 27 children between the age of 1.2 and 11.7 years who were bronchoscopied due to recurrent or chronic respiratory symptoms. The children were re-evaluated 22-80 months after the original bronchoscopy to determine whether they had subsequently developed asthma. The children diagnosed with asthma at follow-up visits showed more eosinophils in the bronchial mucosa and thickness of the subepithelial lamina reticularis when compared to those who did not develop asthma. Eosinophilic inflammation and airway remodeling occur early in the natural history of asthma and are present even before asthma is diagnosed based on clinical symptoms. Saglani et al[27] found that the characteristic pathologic features of asthma in adults and school-age children developed early at 1-3 years of age. The study provided early detection of airway remodeling in preschool wheezers. Recognition of the changes and the significance in clinical practice should emphasize the need for early detection, diagnosis, and intervention of asthma in children. Fedorov et al,[11] using immunohistochemistry, examined the sections of bronchial specimens obtained post mortem or by bronchoscopy from non-asthmatic, moderate, or severe asthmatic children aged 5-15 years. Compared with the finding in non-asthmatic children, the lamina reticularis of asthmatic biopsy sections was found to be thicker with increased deposition of collagen III. There was an asthma-related increase in the level of epidermal growth factor receptor (EGFR). The thickness of the lamina reticularis was correlated significantly with epithelial EGFR. However, submucosal eosinophil numbers were not different in the groups. These data provided the evidence that the epithelium was stressed or injured without significant eosinophilic inflammation in asthmatic children. This change in the epithelial phenotype was associated with collagen deposition in the lamina reticularis, suggesting that the epithelial mesenchymal trophic unit was active early and may contribute to the pathogenesis of asthma. The theory of the epithelial mesenchymal trophic unit, described by Holgate, indicates that asthma is more than just an inflammatory disorder. It requires the engagement of important signaling pathways involved in epithelial repair and tissue remodeling. Pathways such as EGFRs and TGF-betaRs provide targets for developing novel therapies for chronic asthma.[28]

Long-term medication in asthma treatment for airway remodeling

Since airway remodeling starts in childhood and has developed early in the disease process of asthma, this area certainly deserves more efforts and resources.

Asthma medications can be classified as controllers or relievers. Controllers are medications taken on a daily basis for a long-term to keep asthma under clinical

control. It is mainly through the anti-inflammatory effects. Relievers are medications used on an as-needed basis that act quickly to relieve asthma symptoms and reverse broncho-constriction. Controllers include inhaled corticosteroids, leukotriene modifiers, sustained-release theophylline, long-acting β2-receptor agonist (LABA), systemic corticosteroids, anti-IgE (omalizumab), etc.

Apart from airway inflammation, airway remodeling is the main pathological feature of asthma. However, current long-term treatment of asthma emphasizes the control of airway inflammation with less attention to airway remodeling. Pohunek et al[20] suggested that the treatment of asthma using anti-inflammatory medications based on early diagnosis, at the same time, may contribute to the development of airway remodeling.

Inhaled corticosteroids are the most effective controller medication currently available. Corticosteroids inhibit airway inflammation. However, whether the treatment with corticosteroids plays a role in airway remodeling is not clear. Some researchers believe that early intervention can effectively control airway inflammation and prevent the occurrence of airway remodeling, which is the key of the prevention and the treatment of childhood asthma. Beckett et al[19] suggested the indirect effect of steroid on remodeling through the modification of inflammation. There was also *in vitro* evidence for the direct effect of steroids on the cells, cytokines and growth factors. However, early treatment with inhaled steroids may prevent the development of airway events, presumed to be those associated with structural remodeling, which lead to irreversibility in lung function, but do not reverse the changes once they have arisen.[19] Jenkins et al[22] found that airway remodeling of six children with difficult-to-control asthma occurred despite long-term administration of high-dose inhaled and systemic corticoids. Even the patients whose asthma responds to steroid treatment have persistent abnormal airway reactivity.

In a mouse asthma model, the cysteinyl leukotriene (CysLT)1 receptor antagonist montelukast reversed the established increase in airway smooth muscle mass and subepithelial collagen deposition. Key allergen-induced airway structural changes not modulated by corticosteroids were reversed by CysLT1 receptor blockade therapy.[29] In a biopsy study in patients with mild persistent asthma, treatment with montelukast for 8 weeks inhibited the airway remodeling effects (increase in myofibroblasts) following a low-dose allergen challenge.[30] Furthermore, there are occasional case reports indicating that montelukast may have a beneficial effect reversing structural changes within the small airways.[31] However, despite good evidence from both animal experimental models of asthma and human studies, there are still insufficient data to support the clinical role of leukotriene modulator therapy in preventing airway remodeling and its consequences in clinical asthma. Convincing randomized long-term studies are still missing.[32] Also, no studies have been undertaken to look at their effects on airway remodeling.[19]

Combination therapy with inhaled glucocorticosteroids and LABA can control the symptoms of most asthma patients. Fluticasone alone or in combination with salmeterol reduces airway inflammation and airway remodeling by the animal models of asthma.[33] But there is no good evidence from human studies to support the clinical role of combination therapy in preventing airway remodeling. Also, inhaled corticosteroids do not prevent the decrease of lung function[34] and reverse airway remodeling.

Currently, there are no effective treatments that can halt or reverse the changes of airway remodeling and that have effects on lung function.[35] Longitudinal studies have showed that current preventive measures and therapeutic interventions are relatively ineffective in preventing or reversing the development of irreversible airway changes.[36]

Conclusion

In addition to airway inflammation, airway remodeling is one of the main pathological features of asthma. A number of morphological and pathological studies have revealed that airway remodeling can occur not only in adult asthma, but also in childhood asthma. It develops early in the disease process of asthma. Therefore, airway remodeling may be a possible new therapeutic target in asthma. At present, long-term medication in asthma treatment is limited to its anti-inflammatory effect. However, therapeutic interventions that reverse airway remodeling are lacking. Therefore, airway remodeling may become a potential therapeutic target for the treatment of asthma. It is imperative to strengthen the research into asthma airway remodeling.

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