Mechanisms of Airway Remodeling in Asthma

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ABSTRACT
Asthma is a chronic inflammatory disease characterized by reversible airflow limitation and airway hyperresponsiveness. Persistent inflammation in airway tissues may lead to structural changes known as airway remodeling and consequently airway obstruction that is not fully reversible and progressive loss of lung function over time.

It is generally accepted that airway remodeling is closely related to progression of airway hyperresponsiveness, and the severity of asthma. The structural changes observed in chronic persistent asthma, which includes airway smooth muscle hypertrophy and hyperplasia, collagen deposition to sub-epithelial basement membrane, hyperplasia of goblet cells, thickening of airway mucosa and an increase in vascularity, are derived from airway inflammation. For instance, the thickened airway mucosa might be produced by cytokines and growth factors released from inflammatory cells and airway epithelial cells, and associated with bronchial hyperreactivity and asthma severity.

To date, many studies have identified candidate mechanisms and mediators for these observed structural changes, which are thus potential targets in the treatment of asthma. In this review, we describe the recent knowledge of the mechanisms and clinical implications of airway remodeling in asthma.

KEY WORDS
airway remodeling, goblet cells, inflammation, smooth muscle, subepithelial fibrosis

INTRODUCTION
Asthmatic airway inflammation is generally believed to cause tissue injury and subsequent structural changes, so-called airway remodeling (Fig. 1). One of the consequences of prolonged inflammation is thickening of airway wall. Airway wall thickness has been shown to be increased by as much as 50–300% in patients who have died of asthma and by 10–100% in subjects with milder cases,1 and there is evidence that airway wall thickness as measured radiologically correlates with the disease severity and the length of time with disease.

The narrowed airway lumens have been observed in post mortem lung biopsy specimens from patients who had fatal and nonfatal asthma.2 The pathological changes in airways of patients with nonfatal asthma are much less pronounced, with changes seen predominantly in small airways (2–4 mm in diameter).3,4 Pepe et al.5 revealed that a markedly increased muscle mass in airway tissues obtained from subjects with severe asthma compared with those with moderate asthma. In addition, the smooth muscle was located much closer to the epithelium in subjects with severe asthma, perhaps reflecting a phenomenon of migration of smooth muscle cells toward the epithelial surface.

A variety of mediators have been described in airways of asthmatics that could theoretically be relevant to airway remodeling, but it is not entirely known how various stimuli or mediators of the inflammatory response are linked to the processes of airway remodeling. In this review of airway remodeling in asthma, we will focus on structural changes observed in airway epithelium, subepithelium, airway smooth muscle and vasculature, and their proposed mechanisms and clinical implications.

MECHANISMS OF AIRWAY REMODELING
EPITHELIAL DAMAGE, REPAIR AND GOBLET CELL HYPERPLASIA
Airway epithelium plays an important role not only as
Fig. 1 Airway remodeling in chronic asthma includes goblet cell hyperplasia, basement membrane thickening associated subepithelial fibrosis, airway smooth muscle hypertrophy/hyperplasia and angionogenesis.

Barrier from the outer environment but also as the regulator of metabolic and immunologic functions in the airways. It has been reported that epithelial cells are found in increased amounts in asthmatic sputum, and epithelial detachment from the basement membrane is frequently observed in the various models of asthma. There are a lot of inflammatory factors produced by airway epithelial cells, and epithelial damage participates in the proinflammatory processes through cytokines, growth factors, and mediators in asthma patients. The factors contributing to remodeling directly are transforming growth factor (TGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), basic fibroblast growth factor (b-FGF), insulin-like growth factor-1 (IGF-1), endothelin-1 (ET-1), and heparin-binding epidermal growth factor (HB-EGF). These factors have been well known to affect a proliferation of fibroblast and an extracellular matrix production, among which TGF-β produced by airway epithelium might be one of the most important molecules in may of the processes of remodeling.

Airway mucus protects the epithelial surface from injury and facilitates the removal of bacterial, cellular, and particulate debris from the lung. Mucus production is also an important feature of asthma and contributes substantially to morbidity and mortality, especially in more severe disease. Goblet cells and submucosal glands secret mucus, and a high proportion of goblet cells and an enlargement of submucosal glands are associated with hypersecretion of mucus, which may result in the narrowing of airway lumen and, hence, aggravation of airway obstruction. Goblet cell hyperplasia has been consistently demonstrated in mild, moderate and severe asthma (Fig. 2). It is also easily observed in the early stage of allergen challenge in experimental asthma model in mice and guinea pigs. Similarly, enlargement and hyperplasia of mucus glands found in the subepithelium can frequently be seen in asthma.

Goblet cells and mucus glands are the sources of mucin glycoproteins (MUCs) and, to date, 13 MUC genes (MUC1-4, MAU5AC, MAC5B, MUC6-9, MUC11-13) have been identified in human airways. Whereas the expression of several MUC genes in the airway can be detected, MUC5AC gene expression appears to predominate in both asthmatic and nonasthmatic airways but is probably greater in the asthmatic airway. Fahy et al. reported the increased immunohistochemical expression of MUC5AC in bronchial biopsies of asthmatic subjects. In this study, the expression of MUC5AC, MUC2 and MUC4 were similarly increased in the same patients compared with healthy subjects. Another study has shown that the expression of EGF receptor (EGFR) is increased in the airway epithelial cells of asthma patients. This finding seems very important, because EGFR activation can lead to mucin MUC5AC synthesis and goblet cell production in human bronchial epithelial cells in vitro and in rats in vivo. Indeed, Takeyama and colleagues have shown that there is a significant positive correlation between EGFR immunoreactivity and the area of MAC5AC positive staining in the asthmatics and healthy subjects (Fig.
Airway Remodeling in Asthma

Fig. 2 Structural changes in airways of patients died of asthma. A, thickening of (basement membrane (arrow); B, hyperplasia of mucus-producing cells of submucosal gland (arrow); C, airway epithelial cells in healthy subject; D, goblet cell hyperplasia in asthma patient (arrow).

Fig. 3 Correlation between EGFR immunoreactivity and MUC5AC production in airway epithelium. EGFR immunoreactivity showed a significant positive correlation with the area of MUC5AC-positive staining.

3). Furthermore, the expression of EGFR and MUC5AC is upregulated in the epithelium of asthmatics airways at both mRNA and protein levels and is often colocalized in goblet cells. These results suggest that the possible role of EGFR activation in mucin synthesis in asthmatics airways.8

On the other hand, studies on murine asthma model implicate the role of Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) in goblet cell metaplasia. IL-13 increased the proportion of secretory cells, caused overexpression of MUC5AC in the same cells, and consequently altered epithelial cell morphology in primary culture of airway epithelial cells.9 Additionally, Shim et al.10 reported that IL-13 induced goblet cell metaplasia and MUC5AC mucin production in rat airway epithelium, and suggested that these effects may be attributed to EGFR activated by neutrophils recruited into the airways.

The transcription factor STAT-1 is a key molecule in interferon (IFN)-mediated signaling and plays a critical part in the pathogenesis of viral infection. There is evidence that STAT-1 is constitutively activated in epithelial cells from asthmatic subjects but not in those from healthy subjects. STAT-1 levels are correlated with intracellular adhesion molecule-1 (ICAM-1) expression, which is in turn associated with T-lymphocyte accumulation into the tissue.11 Asthma patients have also an elevated level of STAT-6 in the airway epithelium. Other candidate molecules associated with goblet cell hyperplasia are human Ca2+-activated chloride channel-1 (CLCA1) and amphiregulin. Recent studies have demonstrated that the expression of CLCA1 gene is upregulated in goblet cells in patients with allergic asthma12 and that amphiregulin, one of the EGFs, produced by stimulation of mast cell FcεRI enhances the expression of mucin mRNA in airway epithelium.13

SUBEPITHELIAL FIBROSIS
Histologically, reticular basement membrane thickening of airway epithelium is a characteristic feature of asthma, which is not found in chronic obstructive pul-
monary disease or chronic bronchitis. These changes involve the subepithelial space and the thickness can range from 7 to 23 μm in subjects who have asthma, versus 4 to 5 μm in controls. The epithelial basement membrane consists of two layers: shallow layer (basal lamina) and deeper layer (lamina reticularis). When thickened, basement membrane of asthmatic airway is observed with electron microscopy, there is, rather, thickening of the area just below the lamina reticularis, which is true basement membrane. The thickening of subepithelial space corresponds to the deposition of collagen I, III, V and extracellular matrix (ECM), such as fibronectine, laminin and tenascin, and other abnormalities have also been noted in noncollagenous matrix, including elastin, proteoglycans and cartilage. The mechanism of deposition of ECM is thought to be an imbalance between its synthesis and degradation. Collagen deposition in tissues is controlled by the balance of the collagen-degrading matrix metalloproteases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteases (TIMPs). In asthma, the potentially most important members of this family are MMP-9 and TIMP-1. Overexpression of TIMP-1 causes deposition of ECM and thickening of basement membrane by inhibiting degradation of ECM. Studies on asthmatic subjects have revealed the increased production of both MMP-9 and TIMP-1 in sputum and bronchoalveolar lavage fluid (BALF). The ratio of MMP-9 and TIMP-1 in asthmatics is lower than in control subjects and correlates with the degree of airway obstruction. The main source of MMP-9 in asthmatic airways is believed to be eosinophils.

TGF-β is a major cytokine that is synthesized by a variety of cells, such as epithelial cells, macrophages, eosinophils, lymphocytes and fibroblasts, and stimulates the production of ECM. TGF-β1 mRNA appears to be increased in moderate and severe asthmatics compared with normal subjects, and the expression of this cytokine is directly related to the degree of subepithelial fibrosis. Many of the effects of IL-13 may be mediated by the metalloproteinases, IL-13 overexpression is mediated by TGF-β, and TGF-β activation is MMP-9 dependent. It is possible, therefore, that MMP-9 could be a key molecule in the proximal of IL-13-mediated signaling pathway. Smad7 is an inhibitory protein against intracellular signal transduction of TGF-β and is thought to be a modulator of TGF-β actions. Thus, the expression of Smad7 might be involved in the process of thickening of basement membrane. Tenascin is only expressed during tissue repair and this observation solidifies remodeling’s link to chronic inflammation and tissue injury.

Some groups have identified both severe asthmatics with no increase in subepithelial fibrosis and nonasthmatics with increased subepithelial fibrosis. It is also proposed that subepithelial fibrosis could actually be a very early marker for the asthmatic phenotype in children, and that symptom severity, age, or duration is not necessarily related to the degree of basement membrane thickening. Therefore, subepithelial fibrosis might simply represent disordered epithelial-mesenchymal signaling rather than direct response to inflammatory injury. Several papers have demonstrated that thickness of basement membrane has a negative relationship with %FEV1 and provocative dose of methacholine, and other reports have shown that the magnitude of collagen deposition is correlated with the severity of asthma and cough variant asthma.

Myofibroblasts are specialized cells with features of both fibroblasts and myocytes. Structurally, myofibroblasts display a phenotype intermediate between fibroblasts and smooth muscle cells, express α-smooth muscle actin, and have the ability to secrete ECM proteins. In addition, these cells secrete chemokines that can prolong eosinophil survival. Although myofibroblasts are found predominantly in the lamina reticularis, the origin of these cells remains uncertain. Recently, Schmidt et al. described that CD34+ cells expressing procollagen I and α-smooth muscle actin were increased in the bronchial mucosa after allergen challenge in patients with asthma, and Batra et al. reported that the Th2 cytokine IL-4, as well as TGF-β, stimulated fibroblasts to express α-smooth muscle actin.

AIRWAY SMOOTH MUSCLE
An increase in airway smooth muscle mass is the most prominent feature of airway remodeling in asthma. Smooth muscle proliferation consists of hypertrophy (an increase in size of airway smooth muscle) and hyperplasia (an increase in the number of airway smooth muscle). Ebina and colleagues analyzed the distribution of smooth muscle hypertrophy in serial sections of autopsied airway specimen from asthmatic patients by 3-D morphometric technique. They demonstrated two types of airway smooth muscle remodeling in asthmatics: hyperplasia of smooth muscle was found only in the central airways and, in contrast, hypertrophy involved the whole airway tree, including bronchioles. However, the mechanism for this difference is unknown.

The increase in smooth muscle mass is disproportionate to the increase in total airway wall thickness. Recent studies suggest that airway smooth muscle cells might modulate airway remodeling by secreting cytokines, growth factors, or matrix proteins and by expressing cell adhesion molecules and other potential costimulatory molecules. Major factors for airway smooth muscle proliferation are shown in Table 1.

MYOCYTE HYPERPLASIA
There are numerous reviews of the mechanisms regulating airway smooth muscle proliferation.
asthmatic airways, hyperplasia of airway smooth muscle is an important mechanism leading to the increased smooth muscle mass, and it is thought that smooth muscle hyperplasia depends on the stimulation of mitosis and the suppression of apoptosis. The overview of the mechanisms of airway smooth muscle proliferation is shown in Figure 4. There may be at least three major signal transduction pathways associated with airway smooth muscle proliferation, i.e., the effects of mitogens are mediated through different receptor systems: 1) receptor tyrosine kinase (RTK), which is stimulated by PDGF, EGF, bFGF and IGF, 2) G protein-coupled receptor (GPCR), which is stimulated by thromboxane A2, histamine, ET-1 and LTD4, and 3) cytokine receptor which is stimulated by PDGF and IL-1β.

Phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK) activation appears to be the dominant signal transduction pathways for RTK, GPCR, or cytokine receptor-stimulated growth of airway smooth muscle cells. In the downstream of these three receptors, activation of RTK or cytokine receptor induces p21ras activation and stimulates two parallel signaling pathways, ERK or PI3K pathway. Phosphorylation of ERK or PI3K lead to activation of transcription factors such as c-Jun, c-Fos and c-Myc in the nucleus and this may occur via activation of p90 ribosomal S6 kinase. ERK phosphorylates nuclear protein such as cyclin D1 to induce DNA synthesis and cell proliferation. D-type cyclins (cycline D1, D2, and D3) are key regulators of G1 progression in mammalian cells, and cyclin D1 has been the most extensively studied. PI3K phosphorylates membrane phosphoinositides, which function as a second messenger and activate downstream effect of the molecules regulating cell-cycle protein expression and thus modulate cell-cycle traversal. Activation of PI3K is critical for airway smooth muscle cell-cycle progression, although other signaling events are also necessary to promote maximal growth responses. Stimulation of GPCR induces degradation of PIP3 into diacylglycerol and inositol triphosphate, where the former activates protein kinase C, and the latter induces the release of stored Ca2+ from endoplasmic reticulum.

Additionally, STAT3 has been shown to play an important role in the PDGF-induced proliferation of human airway smooth muscle cells. Activation of JAK2 and STAT3 by PDGF appears to be redox dependent and affects the proliferative responses to mitogen independent of ERK activation.

**MYOCYTE HYPERTROPHY**

Airway smooth muscle hypertrophy is indicated by an increase in size of ASM cells. Some mediators, such as IL-1β, IL-6, TGF-β, angiotensin II and cardiotropin I, induce cellular hypertrophy in vitro, although the mechanisms remain unclear. Morphologic studies confirm the presence of airway smooth muscle cell hypertrophy in some, but not all, asthmatic patients. Increased cell size appears to negatively correlate with postbronchodilator FEV1 and distinguishes between severe persistent asthma and milder disease.

In contrast, Woodruff et al. obtained bronchial biopsy specimens from patients with mild to moderate asthma. They found no evidence of airway smooth muscle hypertrophy, although they did confirm the presence of hyperplasia. It is difficult to evaluate airway smooth muscle cell size by 3-D morphometry, and further studies are required in this particular area of smooth muscle cell biology.

**SMOOTH MUSCLE MIGRATION**

Migration of airway smooth muscle cells also likely promotes airway remodeling in chronic asthma. Mukhina and colleagues reported that human airway smooth muscle cells in culture are capable of migrat-

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**Table 1 Major factors for airway smooth muscle proliferation**

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ing, particularly in response to urokinase plasminogen activator. Afterwards, it was proved that PDGF, TGF-β, bFGF and IL-1β increased chemotaxis of airway smooth muscle cells. Recent study has demonstrated that only PDGF, but not EGF or thrombin, induces migration in airway smooth muscle cells.\(^{40}\)

**INFLAMMATORY CELL INFILTRATION**

Airway smooth muscle cells release various cytokines, chemokines, and growth factors through interaction with inflammatory cells, thereby contributing to modulation of airway inflammation and remodeling. These cells have been shown to secrete RANTES, eotaxin, IL-8, monocyte chemotactic protein (MCP)-1, MCP-2, MCP-3, TARC (thymus and activation-regulated chemokine), and GM-CSF in response to TNF-α and IL-1β, and might play a role in promoting both the recruitment and survival of eosinophils through secretion of GM-CSF and IL-5.\(^{41,42}\) Airway smooth muscle cells also express ICAM-1 and VCAM-1, which are inducible by inflammatory mediators, and produce ECM proteins that promote airway remodelling.

Mast cells also play an important role in airway remodelling. Mast cell degranulation and activation by allergen-mediated cross-linking of IgE result in the release of a variety of mediators capable of remodeling airway smooth muscle cells, including tryptase, cysteinyi LTs, and prostaglandin D\(_2\). Upon degranulation, tryptase stimulates proliferation of fibroblasts and myocytes, as well as type I collagen production.\(^{43}\) Activation of mast cell has long been recognized in asthmatic airways\(^{44,45}\) and the number of mast cells is increased within the smooth muscle layer.\(^{46}\) In addition, there is evidence that an increased number of tryptase-positive mast cells are present in airway smooth muscle bundles of asthmatic subjects.\(^{47}\)

Recently, tryptase has been suggested to be an important mediator related to airway remodeling. In our previous study, we measured serum levels of mast cell-derived tryptase in healthy subjects and patients with steroid-naïve mild to moderate asthma, using B12 monoclonal antibody-based immunofluoroassay that detects both monomers and tetramers of α- and β-trypetases. As a result, the tryptase levels were significantly higher in asthmatics than healthy controls, even at asymptomatic periods, and the levels were further increased during asthma attack. There was a negative correlation between serum tryptase levels and FEV\(_1\) determined after treatment with β\(_2\)-agonist (Fig. 5, unpublished data).

Tryptase possess various biological actions, such as proliferation of airway epithelial cells and fibroblasts,\(^{48}\) IL-8 production, and expression of ICAM-1.\(^{49}\) Other studies have shown airway smooth muscle infiltration by mast cells in patients with asthma,\(^{50}\) tryptase could provide a potent stimulus for both DNA synthesis and proliferation of human airway smooth muscles by activating proteinase-activated receptor-2 (PAR-2).\(^{51}\)

Expression of MMP-1 which acts to degrade IGF binding protein, a growth inhibitor is increased in airway smooth muscle cells of asthma patients, and the expression can be induced by various mitogens including LTD\(_4\).\(^{52}\) Progelatinase A (MMP-2) is constitutively released by airway smooth muscle cells but remains inactive because of high levels of tissue inhibitor of MMP-2 on the cell membrane.\(^{53}\) Airway smooth muscle cells also express both pro-MMP-3 and active MMP-3.\(^{54}\) TNF-α stimulates the release of MMP-9, which can degrade matrix and also plays a critical roe in cleaving latent TGF-β to its active form.
Fig. 5  Serum tryptase levels in healthy control subjects and patients with asthma during stable disease and asthma attack. Asthma patients had a significantly higher tryptase level compared with control subjects (left panel). Correlation between serum tryptase levels and FEV1 measured after β2-agonist inhalation. There as a significant negative correlation between these variables, suggesting a possible contribution of tryptase to airway remodeling.

BRONCHIAL NEOVASCULARIZATION
Angiogenesis and microvascular remodeling can be seen in the airways of chronic severe asthma. These changes are likely mediated by multiple factors, and the increased vascularity may be produced by a number of proangiogenic molecules, especially vascular endothelial growth factor (VEGF). VEGF is localized to airway epithelial cells, mononuclear cells, and T lymphocytes. Previous clinical studies suggest an important role of VEGF as a mediator of airway remodeling and increased vascular permeability in asthma. Subsequently, VEGF has been appreciated to be a multifunctional angiogenic regulator that stimulates epithelial cell proliferation, blood vessel formation, and endothelial cell survival. VEGF levels in sputum and BALF are increased in asthmatics, and the levels correlate directly with the disease activity. Bronchial biopsy specimens taken from subjects with asthma reveal an increase in airway vascularity and expression of VEGF and VEGF receptors in the bronchial mucosa. In animal model of asthma, VEGF receptor blockers inhibit both airway inflammation and airway hyperresponsiveness. VEGF also causes a marked increase in inflammation by enhancing the level of Th2 cytokines, especially IL-13 and, vice versa, IL-13 causes an increase in VEGF production. As expected from the IL-13-overexpressing mice, VEGF levels are markedly increased in BAL Fluids after allergen challenge. When a VEGF receptor antagonist was used in vivo, there was a dramatic decrease in airway hyperresponsiveness, which was accompanied by a decrease in IL-13 and IL-4 production. Interestingly, viral infection can also lead to increased VEGF and it has been thought that viral infection early in life predisposes the onset of asthma. Thus, it is possible that VEGF could play a role in the development of asthma. On the other hand, endostatin is proposed to be the most important inhibitory factor of neovascularisation. Proliferation of vascular endothelial cells stimulated by VEGF is potently inhibited by endostatin, but physiologic role of this molecule in airway remodeling remains to be elucidated.

ROLE OF CYTOKINES
Several cytokines, especially Th2 cytokines, have a direct role in propagating the asthmatic inflammatory processes IL-13 is critically important in acute models of allergic inflammation, potently inducing eosinophil-, macrophage-, and lymphocyte-mediated inflammatory responses, subepithelial fibrosis, mucus hypersecretion, and airway hyperresponsiveness. These effects are probably derived from STAT-6 signaling pathway. In addition, IL-4 and IL-13 are also exert di-
rect effects on airway epithelial cells and fibroblasts. These cytokines enhance fibroblast eotaxin release, which potentially explains the accumulation of eosinophils in the lamina reticularis. IL-11 has been known to play a role in airway remodeling, but the increased levels of IL-11 can be found only in the airways of patients with more severe disease, but not those with mild asthma.

CLINICAL IMPLICATIONS: THERAPY FOR AIRWAY REMODELING

It seems very important to prevent airway remodeling in the chronic management of asthma, which leads to prevent progress of the disease severity. A recent study demonstrated that chronic β-adrenoceptor overexpression resulted in airway hyperresponsiveness in mice and appeared to modulate procontractile signaling pathways. We have previously shown that salbutamol, a selective β-adrenoceptor agonist, enhances the growth of cultured human airway epithelial cell lines through stimulation of mitogen-activated protein (MAP) kinase (ERK1/2) cascade. More recently, salbutamol stimulates proliferation of airway epithelial cells and produces airway wall thickening in vivo via MAP kinase-dependent pathway. In the latter study, we have also observed that the salbutamol-induced structural changes can be prevented by the simultaneous use of inhaled corticosteroid. Anti-inflammatory therapy with Inhaled is a main stream of maintenance treatment for all severities of asthma. Regarding the effect on airway remodeling, corticosteroids have been shown to inhibit airway smooth muscle cell migration in vitro, presumably through the inhibition of mitogen-stimulated increase in cyclin D1 protein. It has been well known that corticosteroid binding to the glucocorticoid receptor results in activation of the transcription factor C/EBPα, and a recent study suggests that ASM cells derived from patients with asthma lack the expression of C/EBPα and are therefore resistant to the effects of glucocorticoids on proliferation. Given the ability of VEGF to promote both airway inflammation and remodeling, the data mentioned above suggests a possible role of VEGF antagonists in the treatment of severe asthma, which is resistant to conventional anti-inflammatory agents.

It has been widely recognized that peripheral airway inflammation play an important role in the pathogenesis of asthma, and that the treatment of airway remodeling should be focused on peripheral airways. However a conventional inhaled corticosteroid seems difficult to reach the peripheral airway. To solve this problem, new types of inhaled corticosteroids, such as hydrofluoroalkane-134A (HFA)-beclomethasone has been developed, and several reports showed a reduction of α-smooth muscle actin area in the peripheral airways and an improvement of peripheral airflow limitation after treatment with HFA-flunisolide in patients with mild to moderate asthma. Furthermore, LT receptor antagonists have been demonstrated to inhibit airway smooth muscle proliferation stimulated by EGF, and reduce subepithelial fibrosis and mucus hyper secretion. Therefore, LT receptor antagonists could be of value for preventing airway remodeling in asthma.

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