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Invited Review

Airway Remodeling in Asthma and its Influence on Clinical Pathophysiology

KOHEI YAMAUCHI

Third Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan

YAMAUCHI, K. *Airway Remodeling in Asthma and its Influence on Clinical Pathophysiology.* Tohoku J. Exp. Med., 2006, **209** (2), 75-87 —— Bronchial asthma has been characterized by chronic and allergic airway inflammation, which induces cytological and histological changes in the airway structure over time. These changes have been called airway remodeling, which includes goblet cell hyperplasia, subepithelial fibrosis, and hyperplasia and hypertrophy of airway smooth muscle cells. Airway epithelium in asthma is often occupied with goblet cells, which contain secretory granules. Airway wall thickness increases because of subepithelial fibrosis, and hyperplasia and hypertrophy of airway smooth muscle cells and submucosal glands. Airway remodeling, therefore, can often cause irreversible airflow limitation, an increase of airway hyperresponsiveness and severity of asthma. Recent studies have demonstrated the molecular and cellular mechanisms of goblet cell hyperplasia, subepithelial fibrosis, and hyperplasia and hypertrophy of airway smooth muscle cells. Several lines of evidence suggest that airway remodeling has been induced by cytokines and mediators produced in chronic allergic airway inflammation. Thus, early intervention with inhaled corticosteroid may prevent progress of airway remodeling by suppressing allergic airway inflammation. ———— airway inflammation; goblet cells; subepithelial fibrosis; smooth muscle; airflow limitation

Reversible airflow limitation is the characteristic physiological feature of bronchial asthma. Impairment of pulmonary function in asthma could be reversed to normal level with sufficient therapy. Since inhaled corticosteroid therapy was introduced globally at the end of the last century, symptoms, pulmonary function and quality of life of asthmatics have been dramatically improved.

However, many clinicians noticed that airflow limitation remained in some asthmatics after administration of oral corticosteroid, high dose of inhaled corticosteroid and bronchodilators. In addition, it has been reported that forced expiratory volume in one second (FEV1) in asthmatics declined faster than in normal individuals. Many investigators have focused on airflow limitation, which could not be improved with sufficient asthma therapy (Peat et al. 1987; Lange et al. 1998) (Fig.1). The irreversible airflow limitation is attributed mainly to airway remodeling.

In this review, I describe the effects of airway remodeling on asthma symptoms and pulmo-

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Correspondence: Kohei Yamauchi, M.D., Ph.D., Third Department of Internal Medicine, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka 020-8505, Japan.
e-mail: kyamauch@iwate-med.ac.jp

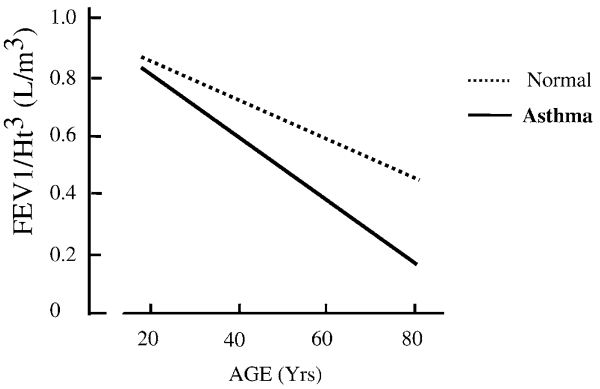


Fig. 1. Impairment of pulmonary function in asthma. Decrease of FEV1 in asthma was faster compared to that in normal individuals. (This figure was referred from Peat et al. [1987], and modified.)

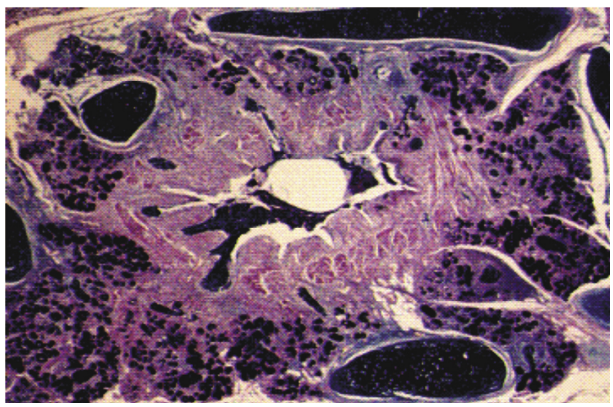


Fig. 2. Highly remodeled airway wall of a bronchus from autopsy of asthma death (courtesy of Dr. Nobukazu Tomochi).

nary function, the mechanism of airway remodeling in asthma and the treatment for airway remodeling.

What is airway remodeling in asthmatics?

Some patients with chronic asthma exhibited persistent airflow limitation even during the period of complete remission or despite treatment with bronchodilators, including theophylline, $\beta 2$ stimulants, and oral corticosteroids (Loren et al. 1978). We also see the patients with moderate/severe asthma showing persistent airflow limitation in asymptomatic period after use of $\beta 2$ stimulants and find many difficult asthmatics among these patients. Their airflow limitation is not fully improved by a high dose of corticosteroid, suggesting that the airflow limitation is not caused by transient airway inflammation (Brown et al. 1984). In fact, pathological analysis on the specimen from transbronchial biopsy or autopsy revealed transformation of epithelium to goblet cells, thickening of epithelial basement membrane, deposition of extracellular matrix in subepithelial layer, hyperplasia of submucosal glands, hypertrophy and hyperplasia of bronchial smooth muscle, and an increase of submucosal vessels which have been thought to be characteristic tissue restructuring in asthma (Hegele and Hogg 1996) (Fig. 2). These structural changes have been called airway remodeling in asthma. Airway remodeling results in thickening of the airway wall and causes irreversible airflow limitation (James et al. 1989). In addition, each component of remodeling influences specific pathophysiology of asthma. The relationship between each pathological change and pulmonary function is important, however, it is not easy to elucidate the relationship because of few opportunities to obtain autopsy samples of asthma death. On the other hand, there have been several reports, which investigated the relationship between the pathological changes on the specimen from transbronchial biopsy and pulmonary functions or asthma symptoms. However, the relationship is not fully understood because of limited numbers of asthmatics receiving transbronchial biopsy and the size of transbronchial biopsy samples in which we could analyze only epithelum and restricted submucosal areas.

According to previous papers, airway remodeling was stronger in the specimen from autopsy than in the transbronchial samples, because a majority of patients with fatal asthma seemed to belong to the severe asthma groups and the patients with mild or moderate asthma tend to accept transbronchial biopsy (James and Carroll 2000). In the experiments with animal models, analyses on a variety of knock-out mice and transgenic mice provided interesting information, although there has been a criticism on the similarity of airway remodeling in animal models with

allergic airway inflammation to that in human beings.

Goblet cell hyperplasia and hypertrophy and hyperplasia of submucosal glands

Proliferation of epithelial cells and prominent goblet cell hyperplasia are characteristic histological findings in asthmatic airway, and these changes are thought to be originated from epithelial damage caused by eosinophils (Büyüköztürk et al. 2004). To date, the study on experimental models with mice demonstrated that Th2 cytokines including interleukin (IL)-4, IL-9 and IL-13 play important roles in induction of goblet cell hyperplasia (Elias et al. 1999). MUC5B and MUC5AC were evaluated as mucin genes expressed in goblet cells. These genes are induced solely by IL-6 or IL-17, but not by IL-4, IL-9, or IL-13, suggesting that each Th2 cytokine may play the particular role in transformation of airway epithelial cells into goblet cells (Chen et al. 2003). Transfer of murine clone, gob-5 gene into the airway, induced MUC5AC gene and goblet cell hyperplasia in the epithelium. Human calcium-activated chloride channel-1 (CLCA1) gene corresponding to murine gob-5 gene is expressed in asthmatic airway, and the expression of this gene is thought to be involved in goblet cell hyperplasia in epithelium (Nakanishi et al. 2001; Hoshino et al. 2002).

Goblet cell hyperplasia in epithelium is one of the important histological changes in asthmatic airway and is observed widely in mild, moderate and severe asthma. It has been also easily observed in the early stage of allergen challenge in experimental asthma model with mice or guinea pigs, and its histological change is reversible. Aikawa et al. (1992) compared the extent of submucosal gland hyperplasia and goblet cell hyperplasia in the airway of the autopsy sample with asthma death to those of asthmatics with other causes of death (Fig. 3). As a result, while there was no significant difference in the areas of submucosal glands between the two groups, the extent of goblet cell hyperplasia in the autopsy with asthma death was significantly higher than that in the autopsy of asthmatics with other causes of death. In particular, goblet cell hyperplasia in peripheral airway was very prominent. These results suggested that the extent of goblet cell hyperplasia in peripheral airway might be one of the risk factors of asthma death. Since occupation of airway lumen with secrete is thought to be one of the causes of asthma death, abnormal airway secretion from massive goblet cells might be involved in asthma death. Furthermore, according to the report by Ordonez et al. (2001), the number of goblet cells was increased significantly in asthmatics, and the stored mucin in the airway was also increased significantly in asthmatics compared to normal individuals, although there was no difference in the size of an individual goblet cell between asthmatics and normal individuals. The amount of the stored mucin in the airway

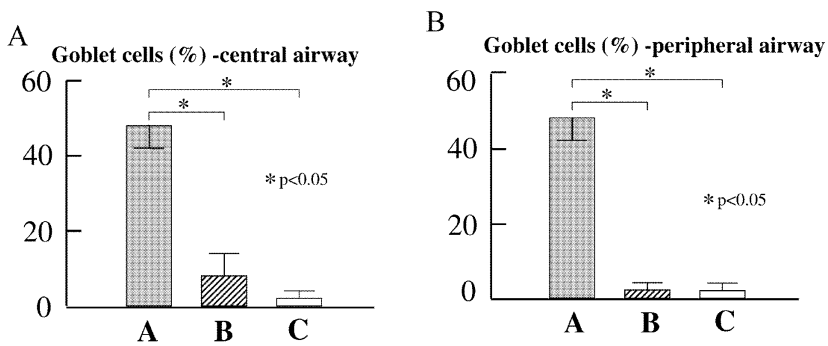


Fig. 3. Goblet cells in central and peripheral airway. The ratio of goblet cells in central and peripheral airway was markedly high in the patients with asthma death. A: the patients with asthma death, B: the asthmatics with other causes of death, C: non-asthmatics. (This figure was referred from Aikawa et al. [1992], and modified.)

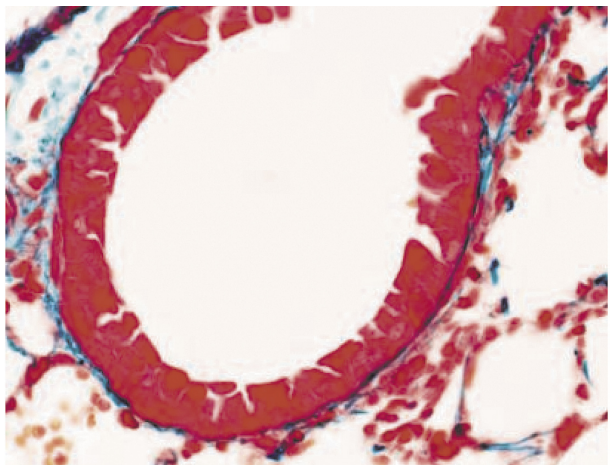
was not different between mild and moderate asthma; however, the content of mucin in induced sputum was significantly higher in the moderate asthma compared to the mild asthmatic group. These results suggested that acute mucin secretion was involved in acute exacerbation in mild and moderate asthma, and chronic mucin secretion might be one of the causes of chronic airflow limitation in moderate asthma. Groneberg et al. (2002) revealed that MUC5AC gene expression was significantly higher in fatal asthma compared to mild asthma according to the analysis on the level of expression of MUC5AC and MUC5B genes.

These series of studies suggest that goblet cell hyperplasia in airway epithelium might be involved in the increase of asthma severity and occurrence of asthma death.

Thickening of epithelial basement membrane and subepithelial fibrosis

Thickening of epithelial basement membrane has been observed as a characteristic remodeling for asthma for a long time but was also found in early asthma (Karjalainen et al. 2000, 2003). Thickening of basement membrane observed with microscopy correspond to the deposition of extracellular matrix (ECM) at subepithelial space observed by electron microscopy, and it is called subepithelial fibrosis (Roche et al. 1989; Jeffery et al. 1992). The deposited ECM consisted of type III collagen, laminin, tenascin and fibronectin (Altraja et al. 1996; Laitinen et al. 1997; Wilson and Li 1997; Hoshino et al. 1998a, b).

The mechanisms of ECM deposition is thought to be an imbalance between synthesis and degradation. When inflammatory cells such as eosinophils transmigrate basement membrane, they produce and secrete matrix metalloproteinase-9 (MMP-9) capable of digesting type IV collagen, which is one of the components of basement membrane (Okada et al. 1997). Over-expression of tissue inhibitors of matrix metalloproteinases 1 (TIMP-1), an inhibitor of MMP-9, causes deposition of ECM and thickening of basement membrane by inhibiting degradation of ECM.



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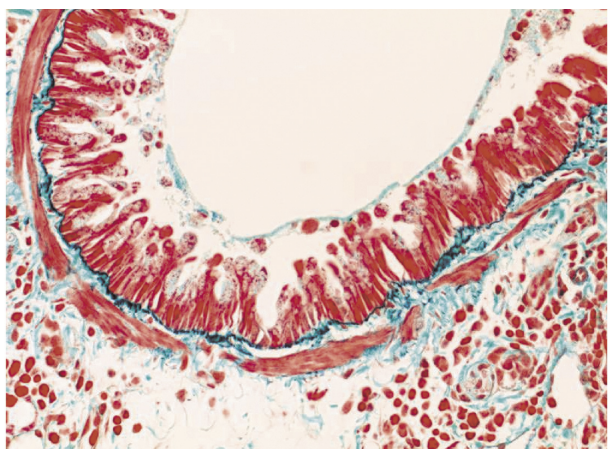

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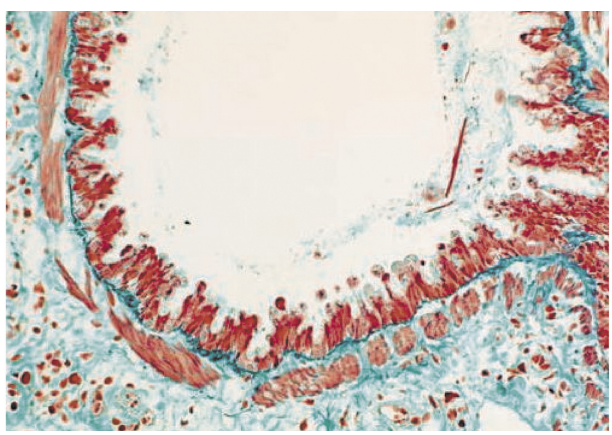

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Fig. 4. Airway remodeling in the experimental asthma model of mice. The mice were sensitized with ovalbumin, and exposed to ovalbumin by daily inhalation. Goblet cell hyperplasia, subepithelial fibrosis and smooth muscle hyperplasia appeared over time.

On the other hand, TGF-β is known to be a cytokine to increase production of ECM. TGF-β was synthesized by a variety of cells, such as macrophages, lymphocytes, fibroblasts, airway epithelial cells, eosinophils, and mast cells (Ohno et al. 1996; Minshall et al. 1997; Vignola et al. 1996, 1997; Hoshino et al. 1998a, b). In the airway, collagens have been thought to be produced mainly by fibroblasts, and the number of myofibroblasts in submucosa is increased in the asthmatic airway. In addition, connective tissue growth factor (CTGF) has attracted attention as a new growth factor which is directly involved in fibrotic response as a down-stream mediator of TGF-β (Grotendorst 1997). Piao et al. (2005) demonstrated up-regulation of CTGF gene expression after allergen exposure in experimental asthma model of ovalbumin-sensitized mice and association between the level of CTGF mRNA and collagen deposition in subepithelial tissue (Fig. 4).

Since the thickening of basement membrane in asthmatic airway was easily observed and can be analyzed quantitatively on the tissue samples from transbronchial biopsy, its relationship with pulmonary functions such as FEV1.0 or airway hyperresponsiveness and asthma severity has been investigated widely. Minshall et al. (1997) demonstrated a significant relationship between the thickness of basement membrane and airflow limitation, and furthermore, a significant relationship between the thickness of basement membrane and strength of TGF-β mRNA expression in eosinophils. Smad7 is an inhibitory protein against intracellular signal transduction of TGF-β, and is thought to be a modulator of TGF-β actions. Nakao et al. (2002) performed immunohistochemistry for Smad7 in the bronchial tissues obtained by transbronchial biopsy from asthmatics and normal individuals, and compared its expression in the airway of these two groups. They demonstrated significant reduction of Smad7 expression in asthmatic airway compared to normals. Furthermore, they revealed a significant negative relationship both between the strength of Smad7 expression and airway hyperresponsiveness, and the strength of Smad7 expression and thickness of basement membrane (Fig. 5). These results suggested that expression of TGF-β and Smad7 might be involved in the progress of thickening of basement membrane and airway hyperresponsiveness. To date, several papers reported that thickness of basement membrane had a negative relationship with % FEV1 and prevocational dose of methacholine (Boulet et al. 1997; Chetta et al. 1997; Shiba et al. 2002).

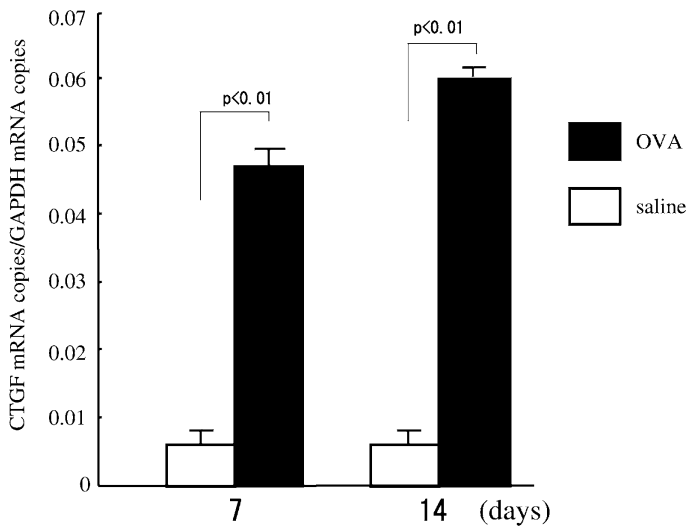

Fig. 5. CTGF mRNA expression in pulmonary tissues in the experimental asthma model of mice. The level of CTGF mRNA in pulmonary tissues from the mice exposed to allergen increased markedly compared with those exposed to saline.

Ward et al. (2001) showed a negative relationship between the distensibility of airway and thickness of basement membrane. Furthermore, Milanese et al. (2001) measured thickness of epithelial basement membrane of bronchial tissues obtained by transbronchial biopsy from patients with mild perennial asthma, perennial allergic rhinitis, seasonal rhinitis and chronic obstructive pulmonary disease (COPD). They revealed that the thickness of basement membrane in the patients with mild perennial asthma and perennial allergic rhinitis was significantly higher than in the patients with seasonal rhinitis and COPD. In addition, thickness of basement membrane in the patients with asthma showed a positive relationship with provocative dose of methacholine in airway hyperresponsiveness (Milanese et al. 2001). These results suggest that reduction of elasticity in airway is associated with progress of thickness of basement membrane.

Several observations suggest a protective effect of airway wall thickening against airway smooth muscle shortening or airway narrowing. In animal models, airway wall thickening (Okazawa et al. 1995) or deposition of extracellular matrix such as collagen or fibronectin in the airway wall after repeated allergen exposure (Palmans et al. 2000), was associated with attenuated airway smooth muscle shortening. Furthermore, Niimi et al. (2003) measured wall thickness of bronchi by helical computed tomography in patients with asthma and demonstrated that airway reactivity negatively correlated with airway wall thickness. Bai et al. (2000) reported that older patients with fatal asthma had more muscle components in the airway wall than younger patients with fatal asthma. Their histological analysis on peripheral airway from autopsy samples revealed that the thickened airway wall consisted of smooth muscle, fibrotic tissue and inflammatory cell infiltration. The fibrosis of the airway wall might protect against a collapse of airway lumen by exaggerated contraction of airway smooth muscle whose mass was extraordinarily increased by hypertrophy and hyperplasia.

It has been difficult for long time to investigate airway remodeling in child asthma because of the rare chance to obtain lung tissue; however, Payne et al. (2003) studied the relationship between airway remodeling and severity of patients with child asthma. To our surprise, the thickness of epithelial basement membrane in the airway of severe child asthma was almost equal to that in adult patients with asthma. Thus, the increase in thickness of basement membrane might be also associated with progress in asthma severity in children. In this regard, we should take airway remodeling into consideration in our chronic management of patients with child asthma.

Hypertrophy and Hyperplasia of Airway Smooth Muscle Cells

Since smooth muscle contraction is one of the causes that induce strong airway narrowing, hypertrophy and hyperplasia of airway smooth muscles has been thought to be important in airway remodeling due to its close relationship with airway hyperresponsiveness and airway narrowing. Airway smooth muscle proliferation has been thought to be induced by growth factors and receptor tyrosine kinases (Hirst et al. 2004). Phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK) activation appeared to be the dominant signal transduction pathways for receptor tyrosine kinase (RTK)-, G protein-coupled receptor (GPCR)-, or cytokine-stimulated growth of airway smooth muscle cells. PI3K phosphorylates membrane phosphoinositides which function as second messengers and activate downstream effector molecules to regulate cell-cycle protein expression and thus modulate cell-cycle traversal (Cantley 2002).

Cohen and colleagues investigated the mechanism of proliferation of bronchial smooth muscle cells in their series of papers and speculated that insulin-like growth factor-I (IGF-I) may induce smooth muscle cell proliferation through activation of a latent form of IGF-I by leukotrienes and MMP (Noveral et al. 1994; Cohen et al. 1995; Rajah et al. 1996).

Airway hyperresponsiveness is a most important physiologic characteristic of asthmatics. Many investigators have tried to elucidate the

origin of increased airway hyperresponsiveness in asthma. Physiological study with excised bronchi could not demonstrate any clear conclusions yet. From histological view points, Ebina et al. (1990) analyzed the distribution of hypertrophic smooth muscles along airways to see where in the bronchial tree asthmatic constrictions mainly occur. They demonstrated two types of smooth muscle hypertrophy in asthmatics (Fig. 6). While hypertrophy of muscles was the most pronounced in larger bronchi in Type I, in contrast, hypertrophy involved the entire range of airways, including the bronchioles in Type II. Their study clearly demonstrated that mass of smooth muscle in the bronchial tree of asthmatics was significantly greater than normal, and leads us to a hypothesis that the origin of increased airway hyperresponsiveness in asthma seems to be attributed to the increased mass of smooth muscle. Supportively, physiological studies could not find any difference of quality in smooth muscle contraction between asthmatics and normals.

On the other hand, since it is not possible to investigate the smooth muscle layers on all tissue samples obtained via transbronchial biopsy from patients with asthma, there have been a few papers describing the relationship between airway smooth muscle remodeling and pulmonary function. Benayoun et al. (2003) analyzed thickness of airway epithelial basement membrane, the amount of collagen III deposition, the numbers of eosinophils, neutrophils and fibroblasts, the areas of submucosal glands and smooth muscle and expression of contractile proteins in the bronchial biopsy samples of normal individuals, and patients with intermittent asthma, mild/moderate asthma, and chronic severe asthma. In their study, the numbers of eosinophils and neutrophils, and the thickness of epithelial basement membrane had increased significantly in the patients with mild/moderate asthma compared to those in the patients with intermittent asthma. Furthermore, while there was not a significant difference in the numbers of eosinophils and neutrophils, and the thickness of epithelial basement membrane between the patients with mild/moderate asthma and those with chronic severe asthma, the amount of collagen III deposition, the number of fibroblasts and the areas of submucosal glands and smooth muscle were significantly higher in the patients with chronic severe asthma than in those with mild/moderate asthma. These histological changes correlated with pulmonary function, and especially the amount of collagen III deposition,

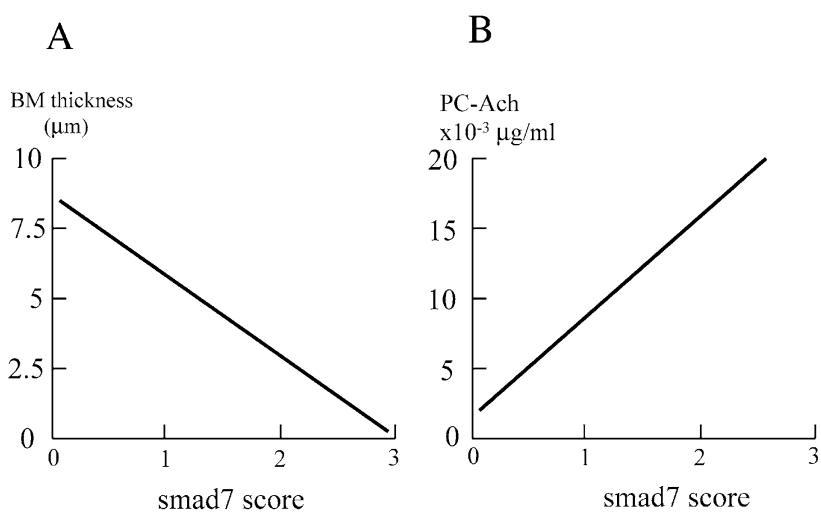

Fig. 6. Airway remodeling and Smad7 expression. A significant negative relationship between thickness of basement membrane and the strength of Smad7 expression (A). A significant positive relationship between airway hyperresponsiveness and the strength of Smad7 expression (B). (This figure was referred from Nakao et al. [2002] and modified.)

the number of fibroblasts, the areas of submucosal glands and smooth muscle and the size of smooth muscle cells correlated with FEV1 after β2 agonist inhalation significantly. Their report confirmed that hypertrophy and hyperplasia of airway smooth muscle induced irreversible airflow limitation, and is an important factor involved in the progress of asthma severity.

Accumulated evidence indicated that eosinophils played critical roles in pathogenesis of asthma (Kayaba et al. 2004); however, effects of anti-IL-5 failed to reduce airway hyperresponsiveness despite decreasing the number of eosinophils in blood (Leckie et al. 2000). Controversy still persists about the role of eosinophils in asthma. It has been demonstrated that peribronchiolar collagen deposition and smooth muscle hypertrophy were lacking in experimental model with eosinophil-deficient mice (Wills-Karp and Karp 2004: Humbles et al. 2004). These papers confirmed the roles of eosinophils in the mouse model of airway remodeling; however, it should be confirmed in the airway of human beings in the near future.

Mast cells are thought to be involved in airway hyperresponsiveness not only by releasing mediators to contract smooth muscle but also by stimulating proliferation of smooth muscles. Gibson et al. (2000) evaluated that the number of airway mast cells correlated with asthma severity and airway hyperresponsiveness.

Brightling et al. (2002) studied the histologic difference between asthmatics and patients with eosinophilic bronchitis who did not exhibit airway hyperresponsiveness. They revealed that the number of mast cells in bronchial smooth muscle was significantly higher in asthmatics compared with the patients with eosinophilic bronchitis.

Berger et al. (2003) proposed an autoactivation loop system whereby mast cells release tryptase upon degranulation, the released tryptase cleaves proteinase-activated receptor-2 (PAR-2) on the surface of smooth muscle cells and induces pertussis toxin-sensitive G-protein activation, which causes subsequent activation of ERK pathway of mitogen activated protein kinase (MAPK) cascade, TGF-β1 and stem cell factor (SCF) protein synthesis is induced and excreted, and these cytokines recruit mast cells. These recruited mast cells can in turn perpetuate the autoactivation loop.

Site of Remodeling in Bronchial Tree

Site of obstruction in the bronchial tree in asthma used be believed to be in the central airway because the total area of the central airway is definitely smaller than that of the peripheral airway. However, measurement of peripheral airway resistance with anterograde catheter revealed that peripheral airway resistance in asthmatics was significantly higher than in normal subjects, suggesting that pathologic abnormality existed in the peripheral airway in asthma (Wagner et al. 1990; Yanai et al. 1992) (Fig. 6). Furthermore, Ohrui et al. (1992) measured hyperresponsiveness to methacholine in the peripheral airway and showed a relationship between hyperresponsiveness in the peripheral airway and irreversible airflow limitation (Fig. 7). Pathological studies on samples from autopsy with asthma death have reported histological changes from the central airway to the peripheral airway (Carroll et al. 1997). However, it is extremely difficult to obtain tissue of the peripheral airway by bronchoscopy. Hamid et al. (1997) obtained lung tissue from asthmatics who underwent an operation, and analyzed inflammatory cells in the peripheral airway. They revealed that inflammatory changes including eosinophil infiltration in the peripheral airway (internal diameter < 2 mm) were more severe compared with those in central airway, suggesting that a major site of pathological abnormalities in asthma is the peripheral airway. Bai et al. (2000) also demonstrated smooth muscle hypertrophy and hyperplasia, tissue fibrosis and inflammatory cell infiltration in the peripheral airway in older patients with asthma death. Peripheral airway was easily obstructed by smooth muscle contraction without cartilage and by mucous plug. Recent reports revealed that asthmatics with peripheral airway obstruction tended to have frequent asthma attacks. However, at present there is little information about airway remodeling in the peripheral airway.

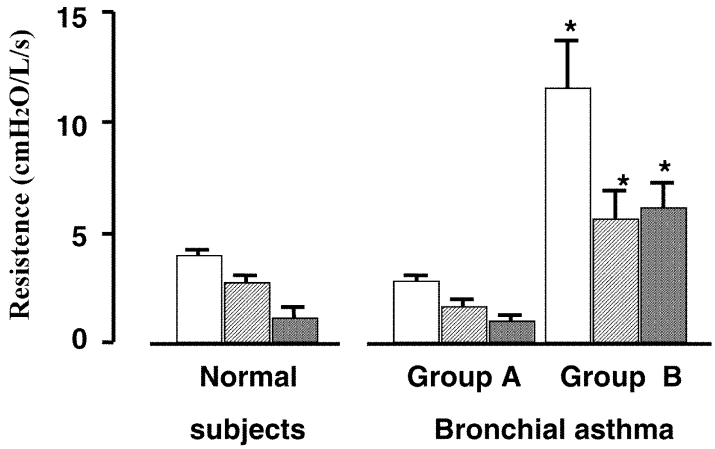

Fig. 7. Absolute values of pulmonary resistance, central airway resistance, and peripheral resistance in normals and asthmatics. Total pulmonary resistance: white column, central airway resistance; dashed column, peripheral resistance; gray column, Group A: asthmatics without airflow limitation; Group B: asthmatics with airflow limitation. (This figure was referred from Yanai et al. [1992] and modified.)

Therapy for Airway Remodeling in Asthma

In asthma, airway remodeling is an important factor to induce irreversible airflow limitation, resulting in progress of asthma severity. To prevent airway remodeling is to prevent progress of asthma severity in the chronic management of asthma. Since it is understood that airway remodeling in asthma proceed in chronic airway inflammation, to control airway allergic inflammation with inhaled corticosteroid is thought to be one of the effective treatments at present. However, once airway remodeling has been formed, it is hard to cure even if we use inhaled corticosteroid. As we know, almost all patients with early asthma categorized into mild asthma, and some of these patients increase their severity over time. For instance, upper respiratory tract infections cause acute exacerbations of asthma (Yasuda et al. 2005).

Since as described above, a major site of airway remodeling is the peripheral airway, a target of treatment for airway remodeling is peripheral airway (Fig. 8). To date, it has been thought that particles of inhaled corticosteroid hardly reached to the peripheral airway. Recently, new types of inhaled corticosteroids, such asHydrofluoroalkane-134A (HFA)-beclomethasone, showed high deposition on peripheral airway and lung parenchyma because of their ultra-fine particles. Hauber et al. (2003) reported that eosinophilic inflammation in the peripheral airway was suppressed by HFA-flunisolide in asthmatics. Bergeron et al. (2005) showed reduction of smooth muscle area and improvement of peripheral airflow limitation with HFA-flunisolide in the patients with mild to moderate asthma, suggesting that treatment with inhaled corticosteroid which

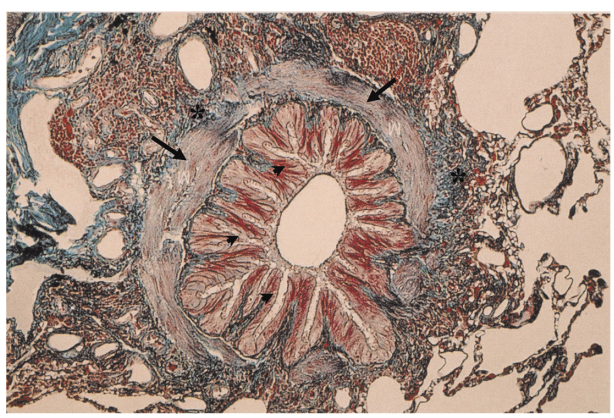

Fig. 8. Highly remodeled airway wall of a peripheral airway from autopsy of asthma death. Tissue was stained with Elastica Goldner. Arrows: hypertrophy and hyperplasia of smooth muscle; arrow heads: goblet cells; *fibrosis (courtesy of Dr. Masahito Ebina).

has smaller particle size is effective to treat airway inflammation and remodeling in the peripheral airway. In addition, leukotriene receptor antagonists have possibility to ameliorate airway remodeling (Henderson et al. 2002; Cakmak et al. 2004).

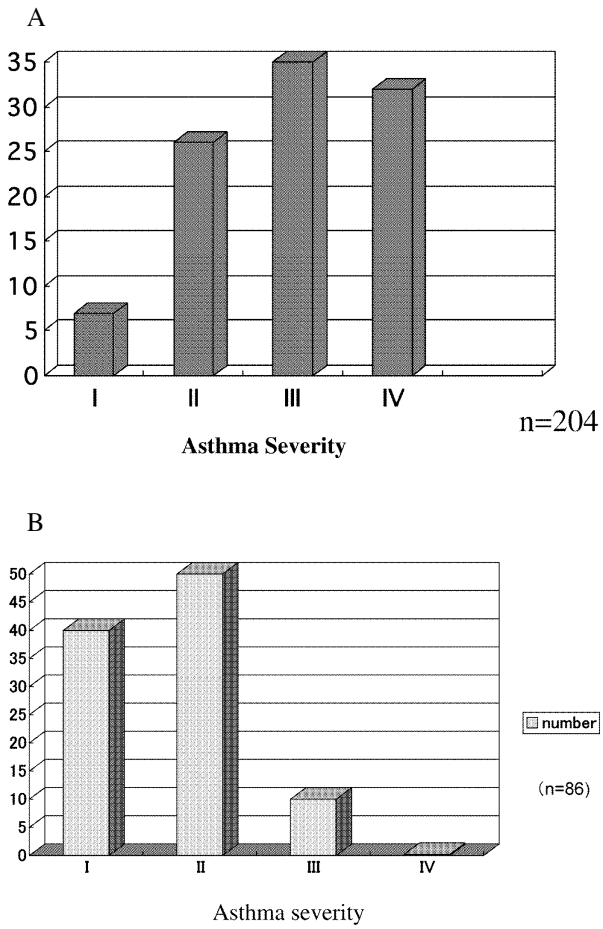

Fig. 9. A: Distribution of asthma severity. Distribution of asthmatics according to asthma severity in the asthma outpatient clinic of Iwate medical University School of Medicine in 2005. The ratio of the patients with severe asthma exceeded more than 30% despite sufficient therapy with high dose of inhaled corticosteroid.
B: Distribution of asthma severity among newly diagnosed asthmatics. Distribution of asthma severity of asthmatics who were newly diagnosed as asthmatic. No severe asthma was recorded in the newly diagnosed asthma from 1995 to 2005.

Early intervention is thought to be an important strategy to prevent airway remodeling with inhaled corticosteroid. Haahtela et al. (1994) presented that the delay to start inhaled corticosteroid therapy induced irreversible airflow limitation, which caused airway remodeling. A major number of patients with severe asthma possess irreversible airflow limitation and have significantly longer duration of asthma, compared to those with mild/moderate asthma. We can speculate that a considerable number of the patients with severe asthma could not receive appropriate asthma therapy, including inhaled corticosteroid in the early stage of asthma. Most clinicians started to adopt inhaled corticosteroid therapy for asthma widely in Japan in the 1990's. However, many patients did not receive inhaled corticosteroid therapy at an appropriate time in their treatment before 1990's and had impaired their pulmonary function, resulting in advancing their asthma severity. As a matter of fact, FEV1 per predicted value is significantly lower in Japanese patients with severe asthma, compared to mild/moderate asthma, and asthma duration in Japanese patients with severe asthma is significantly longer. On the other hand, a significant reduction has been revealed of the ratio of severe asthma in a 10-year study of Japanese asthma patients, who were newly diagnosed as asthma and have had standard therapy for asthma including inhaled corticosteroid (Fig. 9).

In summary, early intervention with inhaled corticosteroid may prevent progress of airway remodeling by suppressing allergic airway inflammation.

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