

Structural consequences of airway inflammation in asthma

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Asthma represents a chronic inflammatory process of the airways followed by healing, the end-result of which is an altered structure referred to as a remodeling of the airways. Repair usually involves 2 distinct processes: regeneration (which is the replacement of injured tissue by parenchymal cells of the same type) and replacement by connective tissue and its eventual maturation into scar tissue. In many instances both processes contribute to the healing response and inflammation. In asthma the processes of cell dedifferentiation, migration, differentiation, and maturation and connective tissue deposition can be followed either by complete or altered restitution of airway structure and function, the latter often seen as fibrosis and increase in smooth muscle and mucus gland mass. These features result in an increased resistance to airflow, particularly when there is bronchial contraction and bronchial hyperresponsiveness. The effect on airflow is compounded by the presence of increased mucous secretion and inflammatory exudate, which not only blocks the airway passages but also causes an increased surface tension that favors airway closure. (*J Allergy Clin Immunol* 2000;105:S514-17.)

Key words: Chronic inflammation, tissue remodeling, asthma

Chronic inflammation is a characteristic of many diseases of the airways. It is invariably associated with healing, which begins very early in the inflammation process. Healing results in the repair and the replacement of dead or damaged cells by viable cells. Repair usually involves 2 distinct processes: regeneration (which is the replacement of injured tissue by parenchymal cells of the same type) and replacement by connective tissue and its eventual maturation into scar tissue.¹ In many instances, both processes contribute to the healing response. Thus a chronic inflammatory disease can be followed by a wide variety of consequences from complete or partial restitution of organ structure and function to fibrosis.²

For many years the major basic mechanisms of asthma were bronchospasm, edema, and hypersecretion; but bronchial inflammation has been largely demonstrated in asthma and appears to be far more complex than a simple eosinophilic inflammation.³ All cells of the airways

are involved.⁴ Cells of the connective tissue and mesenchymal cells (fibroblasts, endothelial cells, smooth muscle) are no longer quiescent and, at least some, appear to be in an activated state.⁵ Inflammatory cells (eosinophils, macrophages, lymphocytes, and mast cells) are increased in numbers and were shown to secrete inflammatory and noninflammatory products involved in inflammation and in healing and fibrogenic growth factors.^{6,7} Extracellular matrix is also involved both at the basement membrane⁸ and submucosa levels, although more data is needed to fully appreciate inflammatory and reparative changes.

Healing and repair, the consequences of chronic inflammation, take place in the asthmatic airways as suggested by the presence of myofibroblasts and the increased number of fibroblasts, collagen hyperplasia, and elastolysis and the deposition of fibronectin and laminin.⁹ It appears that bronchial epithelium regenerates *ad integrum* because there is no major squamous cell metaplasia in asthma. On the other hand, the regeneration of the submucosa appears to be, at least partly, abnormal. These features are seen in almost all patients with asthma whatever the severity or duration or cause of asthma, but their persistence under inflammatory treatment should be investigated. Smooth muscle hypertrophy and mucous gland enlargement, often observed in asthmatic airways, appear to be a permanent abnormality.^{10,11} The wall thickness is greater in subjects with fatal asthma compared with subjects with nonfatal asthma or subjects with no asthma.^{12,13} These findings combine to indicate that asthma is a disease with airway remodeling that may lead to permanent tissue destruction.

STRUCTURAL CONSEQUENCES OF AIRWAY WALL REMODELING

Airway wall thickness and bronchial hyperactivity

In chronic obstructive disorders, bronchial hyperactivity appears to be correlated with airway caliber; histamine or methacholine challenge appears to be associated with the prechallenge FEV₁ level.^{14,15} However, both studies differed because there was a linear relationship between baseline FEV₁ level and response to methacholine in patients with asthma and patients with chronic bronchitis, although the response to methacholine was greater in the patient with asthma than in the patients with bronchitis for any baseline FEV₁ level.¹⁵ On the

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other hand, there was a good correlation between FEV_1 /forced vital capacity and $PD_{20}FEV_1$ histamine values in the 59 subjects with chronic obstructive pulmonary disease but not in the 17 subjects with asthma.¹⁴ Moreover, bronchial hyperreactivity is not only dependent on airway caliber.

Smooth muscle

Benson¹⁶ and Freedman¹⁷ proposed that the same degree of muscle shortening may cause considerably greater luminal narrowing in an airway with a thick wall. This has been confirmed by computer modeling. To examine the interaction between airway smooth muscle shortening and airway wall thickening on changes in pulmonary resistance, a model of the tracheobronchial tree that allows simulation of the mechanisms involved in airway narrowing has been developed.¹⁸⁻²⁰ The model is based on the symmetric dichotomous branching tracheobronchial tree. By simulating progressive airway smooth muscle shortening, realistic pulmonary resistance versus dose-response curves were produced. We conclude that this model provides realistic estimates of pulmonary resistance and shows potential for examining the various mechanisms that could produce excessive airway narrowing in disease. As bronchoconstriction occurs, a marked increase in airway resistance is likely.^{18,21} This computer analysis has also shown that resistance tends to reach a plateau in normal airways whereas it increases progressively in asthma because of airway closure. This particularly occurs in the smaller airways, in which excessive narrowing and closure can be predicted because of smooth muscle shortening.^{19,20} This model has shown²⁰ that even the marked increase in airway wall thickness seen in asthma need not reduce the airway caliber when the airway smooth muscle is at its resting length because this thickening does not encroach on the airway lumen. However, even minimal increases in wall thickness reduce the airway lumen excessively when the muscle shortens. Smooth muscle is capable of shortening up to 70% of its resting length²²; studies by James et al¹⁹ of human lungs have shown that the smooth muscle in the airway of the patient with asthma needs to shorten by only 40% of its resting length to completely occlude the airway lumen. These calculations are consistent with observations made during bronchial challenges. Whereas in normal subjects the fall in FEV_1 level reaches a plateau, in patients with asthma the FEV_1 levels continue to decrease without any plateau occurring.²³

These studies show that the substantial increase in airway wall thickness in asthmatic lungs leads to narrowing and closure of the airway lumen when the smooth muscle shortening is well within its normal range. It also means that the smaller bronchi and bronchioles are particularly vulnerable to closure because they are encircled by smooth muscle.

Increased adventitial thickness was found to increase constriction by reducing parenchymal interdependence. Increased submucosal thickness led to greater luminal occlusion for any degree of smooth muscle shortening.

Increased muscle thickness allowed greater smooth muscle shortening against the elastic loads provided by parenchymal interdependence and airway wall stiffness. We found that for constant airway mechanics, as reflected by the passive area-pressure curves of the airway, the increased muscle mass is likely to be the most important abnormality responsible for the increased resistance observed in response to bronchoconstricting stimuli in asthma and chronic obstructive pulmonary disease. For a given maximal muscle stress, greater muscle thickness allows the development of greater tension and thus more constriction of the lumen.²⁴

Mucous glands

Widespread occlusion of the lumen of conducting airways by mucous plugs is common in fatal asthma. Most patients who died of fatal asthma have excessive mucus production^{25,26} leading to endobronchial mucus suffocation. Over 50% of the airway may be occluded by mucus during fatal asthma.¹³ The large and small airways are stuffed with secretions so viscid that patients are poorly responsive to high-dose inhaled bronchodilators.²⁷ Mucus plugs occur in airways of all sizes, from the second generation airway to bronchioles,²⁸ and consist of fluid, proteins, migrating inflammatory cells including degranulated eosinophils releasing eosinophilic cationic protein and major basic protein and desquamated epithelium. Charcot-Leyden crystals composed of pure eosinophil lysophospholipase²⁹ associated with eosinophilic membranes³⁰ are found in plugs. Distal bronchioles contain Curschmann spirals,³¹ which are small whorled mucus strands twisted in a common direction with a centrally highly refractile densely coiled or braided core,³² representing the cast of the airway.

CLINICAL AND RADIOGRAPHIC CORRELATES OF AIRWAY REMODELING

Abnormal pulmonary function in patients with asthma

For decades, asthma has been considered a completely reversible obstructive disease; in most patients, complete reversibility of long-standing abnormal spirometric measurements, such as FEV_1 level, may be observed after bronchodilators and/or a course of corticosteroids. On the other hand, many patients with asthma (both children and adults) have evidence of residual airway obstruction,³³⁻³⁵ which may even be noticed in some asymptomatic patients.³⁶ However, this irreversible component of the airway obstruction is more prominent in patients with severe disease and even persists after an aggressive anti-inflammatory treatment or a long-term treatment with inhaled corticosteroids.³⁷ Moreover, it may be observed months after the cessation of asthmatic symptoms in asymptomatic patients.^{33,36,38} Patients with asthma, children or adults, are heterogeneous with regard to complete reversibility of airflow limitation. Studies in which lung function changes have been examined showed that FEV_1 level was decreased mainly in subjects

with persistent asthma, but objective measures of the small airway were usually not performed.^{36,39,40} Wagner et al⁴¹ have shown that peripheral lung resistance (studied with a bronchoscope wedged in a subsegmental bronchus) was increased in asymptomatic patients with asthma with normal FEV₁ levels and that this physiologic abnormality was not decreased by isoproterenol. This study is of importance because the FEV₁, but not the FEF_{25-75%}, level of the patients was within normal range, suggesting that changes in the mechanical properties of the small airway only have a small influence on the overall pulmonary function.

During adult life, asthma is associated with an increase in the rate of decline in FEV₁ level.⁴²⁻⁴⁴ In the middle-aged and elderly smokers, it is virtually impossible to separate chronic bronchitis and asthma by means of FEV₁ level. Bronchial hyperresponsiveness appears to be inconsistently associated with an increase in the rate of decline of lung function.^{39,45} However, the effect of asthma is variable, and not all subjects with asthma have steep rates of decline. It appears that asthma starting after the age of 50 years elicits a steeper rate of decline than asthma with an earlier onset.⁴⁶ It has also been shown that patients with nonallergic asthma have a steeper rate of decline of FEV₁ levels.^{44,47}

The prognostic implications of incomplete reversibility seen in some patients with asthma remain to be determined, but chronic sequelae of asthma may lead to complications including severe symptoms and work disability.⁴⁸ Whether residual irreversible air-flow limitation in individuals with asthma or a history of asthma could have been prevented either by aggressive pharmacologic treatment or by limitation of exposure to smoke or other noxious environmental agents is another question that needs more data to be fully answered.^{37,49-52}

Taken together, these studies indicate that many patients with asthma have physiologic abnormalities even when they are asymptomatic and/or receiving anti-inflammatory treatment. These may be due to bronchial inflammation and airway remodeling that is shown to be present in most patients even when they are asymptomatic.

Radiographic findings

Paganin et al⁵³ studied chest radiographs and high-resolution computed tomography scans in 57 adult patients with chronic asthma of variable severity and cause. Computed tomography scans were abnormal in 71.9% of the patients with asthma. Reversible abnormalities included mucoid impactions, alveolar syndrome, and lobar collapse. Irreversible abnormalities included bronchiectasis⁵⁴ without clinical implication, bronchial wall thickening, sequellar line shadows, and emphysema. These were significantly more prevalent in severe asthma than in mild asthma. Most of these abnormalities were likely to be related to bronchial destruction. This study showed that destructive lesions are observed in asthma. Most of these lesions are related to bronchial abnormalities and emphysema is only minimally present, in most cases because of a cicatricial peribronchial fibrosis. These

results are in accord with the study of Neeld et al⁵⁵ in a smaller number of patients with asthma. In a further study that examined the patterns of high-resolution computed tomography scans in 126 patients with asthma of variable severity and cause, it was found that there was an increase in permanent abnormalities depending on the severity of asthma and that patients with nonallergic asthma had a significantly greater number of permanent abnormalities than those patients with allergic asthma.⁵³

Modulation of airway remodeling by drugs

The effects of anti-inflammatory drugs on airway remodeling are not fully understood yet.⁵⁶ In occupational asthma, cessation of exposure to isocyanates leads to a reduction in the size of the basement membrane.⁵⁷ In chronic asthma, except in 1 study,⁵⁸ it has been shown that inhaled steroids do not reduce the size of the basement membrane,⁵⁹ even after a long-term treatment course.^{60,61}

Prevention of airway remodeling

The effect of anti-inflammatory treatment on the natural course of asthma is still a matter of debate because the longest prospective studies available do not exceed 5 years. It seems that inhaled corticosteroids can reduce the accelerated decline of the pulmonary function both in children and adults,^{50,51,62,63} but the effects appear to be incomplete in some patients.³⁷ However, there is no definite proof that undertreatment of asthma would induce deterioration in the long term. Moreover, it is not known whether very long treatment courses with inhaled steroids (for 20-30 years) may not induce bronchial and systemic side effects, especially when the treatment is started very early in life.

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