

New millennium: The conquest of allergy

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Series editors: Donald Y. M. Leung, MD, PhD, Stanley J. Szefer, MD, and Harold S. Nelson, MD

Tissue remodeling as a feature of persistent asthma

Antonio M. Vignola, MD, PhD,^a Johan Kips, MD,^b and Jean Bousquet, MD, PhD^c

Palermo, Italy, Ghent, Belgium, and Montpellier, France

A chronic inflammatory process is almost invariably associated with tissue damage and healing. Healing results in repair and 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. In many instances both processes contribute to the healing response. Chronic inflammatory disease can therefore lead to a wide variety of consequences, from complete or partial restitution of organ structure and function to fibrosis. Asthma is characterized by a chronic inflammatory process of the airways. The ensuing healing process results in structural alterations referred to as a remodeling of the airways. The mechanisms underlying these structural alterations are still largely unknown. They are likely to be heterogeneous, leading—through the highly dynamic process of cell de-differentiation, migration, differentiation, and maturation—to changes in connective tissue deposition and to the altered restitution of airways structure, resulting in mucus gland hyperplasia, neovascularization, fibrosis, and an increase in smooth muscle mass. (*J Allergy Clin Immunol* 2000;105:1041-53.)

Key words: Asthma, airway remodeling, inflammation, airway obstruction, bronchial hyperresponsiveness

Remodeling is defined in the *Concise Oxford Dictionary* (10th edition, 1999) as “model again or differently, reconstruct.” This is a critical aspect of wound repair in all organs, representing a dynamic process that associates matrix production and degradation in reaction to an inflammatory insult that leads to a normal reconstruction process (model again) or a pathologic one (model differently).¹ Structural remodeling in airway diseases was initially proposed to describe changes induced in endothelial cells and extracellular matrix (ECM) by injury of the

Abbreviations used:

BAL:	Bronchoalveolar lavage
BHR:	Bronchial hyperresponsiveness
ECM:	Extracellular matrix
HRCT:	High-resolution computed tomography
IGF:	Insulin growth factor
MMP:	Metalloprotease
TGF- β :	Transforming growth factor- β
TIMP:	Tissue inhibitor metalloprotease

pulmonary circulation. It was then extended to many other pathologic situations, including asthma.²

The regeneration process in asthma follows the natural course of chronic inflammation and results in either tissue repair, a tightly regulated salutary biologic response, or abnormal remodeling, an unregulated pathologic process. This appears to be heterogeneous, leading—through a dynamic process of cell de-differentiation, migration, differentiation, and maturation—to changes in connective tissue deposition and to permanently altered airways structure.³

For decades, asthma has been considered a condition of reversible airflow obstruction, and in the majority of patients, complete reversibility of long-standing abnormal spirometric measurements, such as FEV₁, may be observed after treatment. However, many patients with asthma, both children and adults, have evidence of residual airway obstruction, which may be detected even in patients without symptoms. This clinically demonstrable irreversible component of airways obstruction was also reflected in pathologic findings observed as early as the turn of the century and already proposed in the definition of asthma in 1962.⁴ However, these features were almost completely ignored for a long time, and the concept of airway remodeling in asthma was only proposed in 1992.² The clinical and functional consequences of airway remodeling are now better understood, but the prevention and treatment are still unclear.

PATHOGENIC MECHANISMS

Origin and fate of the inflammatory infiltrate in asthma

Accumulation of inflammatory cells in the bronchial mucosa is characteristic of asthma. The tissue infiltration of cells may involve both recruitment of mature cells from

From ^aIstituto di Fisiopatologia Respiratoria, Palermo, Italy; ^bDepartment of Respiratory Diseases, Ghent University Hospital, Ghent, Belgium; and ^cCliniques des Maladies Respiratoires and INSERM U454, CHU, Montpellier, France.

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Reprint requests: Jean Bousquet, MD, PhD, Cliniques des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire, 34295 Montpellier Cedex 5, France.

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the blood stream and proliferation of their progenitors in the submucosa. The survival of these cells is influenced to a large extent by the micro-environment within the airway wall. As in most organ systems, superfluous and damaged cells are removed by programmed cell death or "apoptosis."⁵ In contrast with necrosis, which may also be seen at inflamed sites, apoptosis represents a granulocyte fate, which by a number of mechanisms would tend to limit inflammatory tissue injury and promote resolution rather than progression of inflammation. Several components in the micro-environment are known to influence apoptosis and hence the survival of inflammatory cells. Increased survival has been reported by interaction with other cell types such as epithelial cells, cytokines, and growth factors.⁶ GM-CSF and IL-5 are among the cytokines that reduce eosinophil apoptosis.⁷ Enhanced survival by causing more pronounced tissue damage can contribute to airway remodeling.⁸ In one study a correlation was found between the severity of asthma, GM-CSF immunoreactivity, and eosinophil survival.⁹ In addition, the numbers of apoptotic eosinophils and macrophages were found to be significantly lower in patients with asthma than in healthy subjects and patients with chronic bronchitis⁹ (Fig 1). Because both macrophages and eosinophils are able to release profibrotic growth factors, it is likely that the increased recruitment and survival of these cells in the inflamed airways of patients with asthma may contribute to the development of structural changes in the bronchial mucosa.⁹⁻¹¹

Interdependence between inflammation and remodeling

The inflammatory process underlying asthma results from a highly complex interaction of various cell types.¹² The structure of tissue components within the airway wall does not represent a biologically inert framework. Apart from inflammatory cells such as eosinophils, activated T cells, mast cells, and macrophages, structural tissue cells such as epithelial cells, fibroblasts, and smooth muscle cells can also play an important effector role through the release of a variety of mediators, cytokines, and chemokines.¹³ This results in an acute inflammatory response characterized by vascular leakage, mucus hypersecretion, epithelial shedding, and widespread airway narrowing. At the same time, through the release of mediators, cytokines, chemokines, and growth factors, these cells cause persistence of the inflammatory infiltrate and induce structural changes in the airway wall.

In addition, components of the ECM can also profoundly interact with inflammatory cells.¹⁴ Among their many effects, such as forming a reservoir for cytokines and growth factors,^{15,16} proteoglycans and glycosaminoglycans serve as ligands for cell adhesion molecules on inflammatory cells, including integrins or homing receptors, and can thus influence trafficking of cells.^{17,18} ECM proteins can also activate granulocytes, increasing mediator release and enhancing their survival.¹⁹⁻²¹ Conversely, several inflammatory mediators have a known proliferative effect on airway smooth muscle and induce the syn-

thesis of ECM proteins and growth factors in fibroblasts and epithelial cells.^{22,23} In addition, metalloproteases (MMPs) selectively degrade ECM components and have been implicated in angiogenesis and in smooth muscle hyperplasia by cleaving growth factors such as insulin growth factor (IGF).^{24,25} MMPs also play a crucial role in the trafficking of inflammatory and structural cells.²⁶

It therefore appears that airway inflammation and remodeling are interdependent processes that clearly influence the clinical long-term evolution of asthma.

Cells of the inflammatory infiltrate involved in remodeling

Bronchial epithelial cells play an active role in the development of airway inflammation and remodeling in asthma.²⁷ Bronchial epithelial injury initiates a complex series of repair mechanisms, one of which is the re-epithelialization of a denuded luminal surface. Regenerative changes are sometimes observed, as demonstrated by varying stages of ciliogenesis in the non-ciliated "metaplastic" surface epithelium.²⁸ It is likely that bronchial epithelial cells initially affected by bronchial injury may be able to initiate repair of an injured area by producing chemotactic factors for epithelial cells. Epithelial cells in asthma express several membrane markers, including adhesion molecules,²⁹ and release a wide spectrum of molecules participating in airway repair including fibronectin, growth factors,^{10,13,27} cytokines (including IL-9, IL-16,³⁰ IL-11,³¹ and IL-18³²), or chemokines such as GM-CSF^{33,34} and eotaxin.^{35,36}

Dendritic cells are the primary antigen-presenting cells in the airways.³⁷ After antigen uptake, they migrate from the airway mucosa toward the regional lymph nodes and mature into effective antigen-presenting cells.³⁸ Dendritic cells can drive either T_H1 or T_H2 responses, depending on the cytokine milieu and co-stimulatory factors, such as IL-12, IL-10, and prostaglandins,³⁹ and therefore play a central role in directing and consolidating the immune response in asthmatic airways.

Activated macrophages have the potential to secrete a wide variety of products, many of which play a major role in the pathogenesis of injury and repair.⁴⁰ Alveolar macrophages can synthesize and secrete plasminogen activator and a group of metalloproteinases that have the capacity to degrade various ECM macromolecules including elastin. Macrophages may also be involved in the regulation of airway remodeling through the secretion of growth factors such as platelet-derived growth factor, basic fibroblast growth factor, or transforming growth factor- β (TGF- β),¹¹ which are possibly involved in fibrosis.

Fibroblasts play a key role in the remodeling process. They produce collagen and reticular and elastic fibers, as well as proteoglycans and glycoproteins of the amorphous ECM.⁴¹ Their biologic activity is regulated by a range of cytokines and growth factors.⁴² Although they are regarded as fixed cells of the ECM, they retain the capacity for growth and regeneration and may evolve into various cell types including smooth muscle cells.⁴³ Myofibroblasts can potentially contribute to tissue remodel-

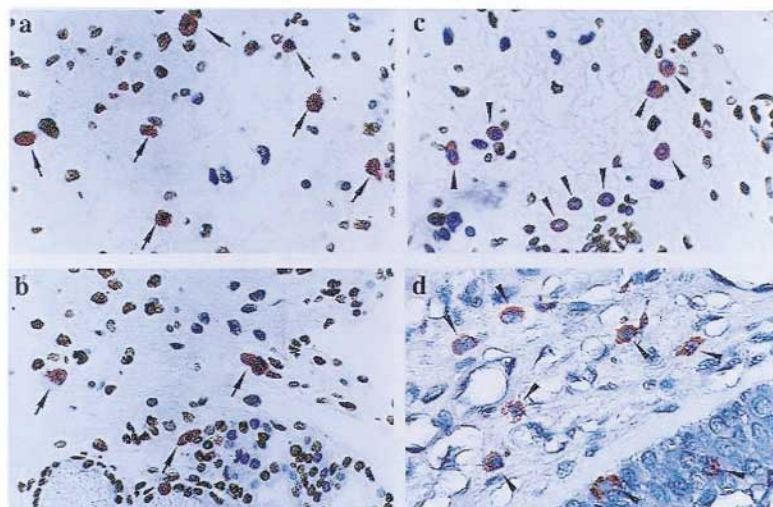


FIG 1 Identification of apoptotic eosinophils and macrophages in bronchial biopsy specimens from patients with asthma and chronic bronchitis. Apoptotic cells are identified by dark brown nuclear staining with the TUNEL (terminal deoxynucleotidyl transferase—mediated dNTP nick end-labeling) technique. Eosinophils and macrophages are identified by red cytoplasmic staining caused by the alkaline phosphatase—anti-alkaline phosphatase immunoreactivity with EG2 or CD68 mAbs (original magnification $\times 200$).

eling by releasing ECM components such as elastin, fibronectin, and laminin.⁴⁴ Increased numbers of myofibroblasts are found in the airways of patients with asthma, and their number has been correlated with the size of the basement reticular membrane.⁴⁵ After bronchial allergen challenge, myofibroblast numbers are increased and the cells undergo a differentiation process.⁴⁶ It appears that the ability of myofibroblasts to promote tissue remodeling in asthma is profoundly influenced by the degree of activation and damage of bronchial epithelial cells releasing basic fibroblast growth factor, platelet-derived growth factor, IGF-1, TGF- β 2, and endothelin-1.^{22,47}

T cells may play a role in pulmonary fibrosis through their cytotoxic effect on lung parenchymal cells.⁴⁸ Recently, an increase in the CD4/CD8 ratio has been demonstrated to be associated with asthma symptoms and airway fibrosis.⁴⁹ Although it is still unknown whether T lymphocytes can directly cause tissue damage and remodeling in asthma, these cells contribute to the pathogenesis of structural changes of the airways by orchestrating the recruitment and activation of inflammatory cells.⁵⁰

Eosinophils can release cytokines, growth factors,^{51,52} and elastase, which may be involved in remodeling and fibrosis. Eosinophil products stimulate fibroblasts *in vitro*.⁵³ Eosinophils appear to be involved in pulmonary fibrosis⁵⁴ and are a source of TGF- β in bronchial biopsy specimens obtained from asthmatic subjects.^{10,55}

Mast cells appear to have an important role in pulmonary fibrosis.^{56,57} Mast cell products stimulate migration and proliferation of fibroblasts.^{58,59} Mast cell lines can release components of basement membranes such as laminin and collagen IV.⁶⁰ Tryptase, a mast cell–derived mediator, is able to activate fibroblasts.⁶¹

Polymorphonuclear neutrophils have long been regarded as terminally differentiated cells, incapable of protein

synthesis and fulfilling only a passive effector role in inflammation through phagocytosis and the release of preformed enzymes and cytotoxic compounds. However, neutrophils can release a wide variety of enzymes including ECM-degrading proteases and elastase, oxygen free radicals, and cytokines such as IL-1, TNF- α , and IL-6.⁶² Neutrophils are increased in the airways of patients with severe asthma,⁶³ suggesting that these cells might participate in the airway remodeling in asthma.

Smooth muscle cells have recently been implicated as inflammatory cells in asthma.¹³ In addition to contractile responses and mitogenesis, airway smooth muscle cells have synthetic and secretory potential with the release of RANTES.⁶⁴ They may participate in chronic airway inflammation by interacting with both T_H1- and T_H2-derived cytokines to modulate chemoattractant activity for eosinophils, activated T lymphocytes, and monocytes/macrophages. Smooth muscle cells also have the potential to alter the composition of the ECM environment and orchestrate key events in the process of chronic airway remodeling.⁶⁵

DEMONSTRATION OF AIRWAY REMODELING IN ASTHMA

The airways in asthma display various structural alterations, which can all contribute to an overall increase in airway wall thickness^{66,67} (Fig 2).

Extracellular matrix

The ECM is a complex and dynamic meshwork influencing many cell biologic functions such as development, migration, and proliferation.^{68,69} The ECM also plays an essential supporting structural role, which differs somewhat in the 3 physiologic zones of the lung⁷⁰:

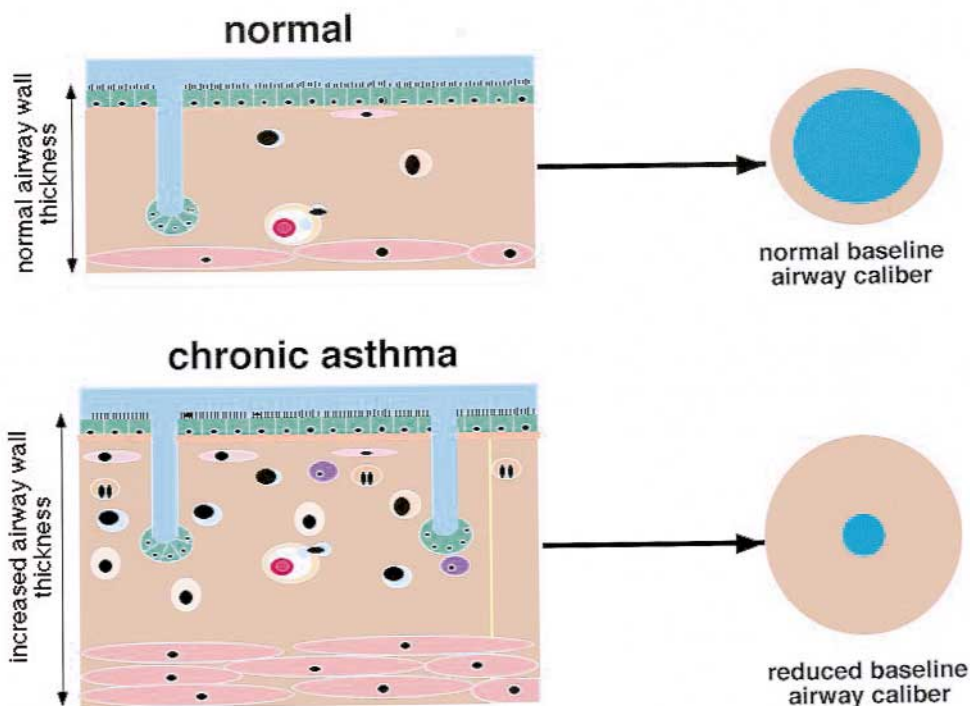


FIG 2. Relationships between airway wall thickness and baseline airway caliber. Airways in asthma display various structural alterations, all of which can contribute to an overall increase in airway wall thickness, leading to a reduced airway caliber.

the proximal conducting airways and vasculature, the distal gas-exchanging respiratory zone (alveoli), and the intervening transitional zone (respiratory bronchioles). In the conducting airways, the ECM of the rigid cartilage (composed largely of proteoglycans and collagen) and the more flexible interstitial tissue support the adjacent epithelial and smooth muscle cells. The ECM both allows some mobility to regulate airway and vascular diameter and acts as an essential stabilizer for preventing airway collapse during expiration. In the respiratory and transitional zones, the ECM is more dynamic to accommodate the constant fluctuations in alveolar volume that accompany inspiration and expiration. The macromolecules that constitute the ECM are secreted locally and consist of fibrous proteins (fibronectin and laminin) embedded in a hydrated polysaccharide gel containing several glycosaminoglycans including hyaluronic acid. The ECM is a dynamic structure, and an equilibrium between synthesis and degradation of ECM components is required for the maintenance of its homeostasis (Fig 3). The ECM can be divided into 2 categories: the basement membrane and the interstitial matrix.

Thickening of the reticular basement membrane (ie, lamina reticularis)

The basement membrane of surface epithelium is composed of 2 layers: the basal lamina (referred to as the "true" basement membrane) and the lamina reticularis. The basal lamina is of normal thickness in asthma. However, thickening of the lamina reticularis is a characteristic feature of

the asthmatic bronchus, occurring early in the disease process. It appears to consist of a plexiform deposition of immunoglobulins and/or collagen I and III and fibronectin⁷¹ but not of laminin.⁷² These proteins are likely produced by activated myofibroblasts,⁴⁵ leading to a so-called fibrosis of the airways. In some studies, the thickening could not be related to the severity, duration, or etiology of asthma,⁷³⁻⁷⁵ whereas a correlation with the severity of the disease has been observed in one study.⁷⁶ Patients with rhinitis also have subepithelial fibrosis of the bronchi with a deposition of type I and III collagen and fibronectin.⁷⁷ However, these features are less marked than in asthma.

Interstitial matrix

Remodeling processes of the interstitial matrix are less well documented than the thickening of the reticular basement membrane. However, many features can be observed.

Elastic fibers. Most patients with asthma have an abnormal superficial elastic fiber network with fibers appearing fragmented.⁷⁸ The deeper layer of elastic fibers is also abnormal in most patients with asthma; fibers are often patchy, tangled, and thickened, suggesting that fibers from patients with asthma have the appearance of solar elastolysis in skin. Electron microscopy studies show that a severe elastolytic process occurs in patients with asthma, and in some patients, disruption of fibers has been observed. In fatal asthma, elastic fiber fragmentation has also been found in central airways and was associated with marked elastolysis.⁷⁹ These bundles appear to be hypertrophied in asthmatic patients as a result of the

ECM remodeling in asthma

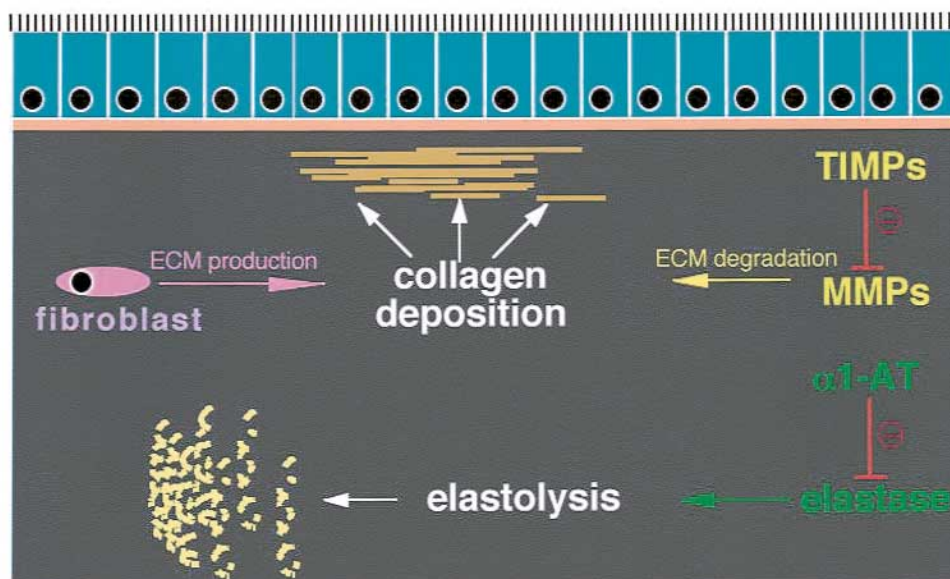


FIG 3. Involvement of proteases and anti-proteases in ECM remodeling in asthma. Processes leading to an increased ECM deposition may occur concomitantly with processes involved in ECM degradation. The balance between MMPs and TIMPs and of elastase and α_1 -AT (α_1 -antitrypsin) control the rates of ECM deposition and degradation.

increased amount of collagen and myofibroblast matrix deposition that occurs during the exaggerated elastic fiber deposition.⁸⁰ The increased elastolysis in asthma is part of a more complex process that regulates, in a dynamic fashion, the size of a submucosal network formed by elastic fibers dispersed in a collagen and myofibroblast matrix, which are intimately interrelated and constitute longitudinal bundles in the bronchial tree.

Hyaluronic acid. Hyaluronic acid levels have been found to be increased in the bronchoalveolar lavage (BAL) fluid of patients with asthma.⁸¹ Moreover, there was a significant correlation between hyaluronic acid levels and the severity of asthma or the level of eosinophilic cationic protein, suggesting a common activation of cells releasing these compounds.

Collagen and proteins. In the submucosa of patients with asthma, electron microscopy studies show that collagen is not completely normal. In some patients, hyperplasia of collagen fibers can be observed.⁸⁰ These fibers may be irregularly dispersed, but the exact nature of collagen is not completely characterized. Fibronectin (Fig 4), laminin, and tenascin deposits in the submucosa were found in the biopsy specimens of patients with asthma but not in those of healthy subjects.^{72,82} Fibronectin levels are increased in BAL fluid of patients with asthma and correlate with the levels of TGF- β .¹¹

Fibrogenic growth factors

Over the past few years, expression of fibrogenic growth factors in bronchial biopsy specimens obtained

from asthmatic airways has been increasingly investigated. Increased expression of IGF-1, EGF, and TGF- β in biopsy specimens or BAL has been reported.^{10,11,55,83-87} TGF- β expression was found to correlate with the degree of subepithelial fibrosis¹⁰ (Fig 5) and to be significantly increased in patients with severe asthma, with a rich eosinophilic infiltration of the airways.⁸³ However, other studies have not shown any difference in expression of platelet-derived growth factor, TGF, epidermal growth factor, or IGF in tissues from patients with asthma as compared with healthy control subjects^{15,88} or patients with chronic bronchitis who clearly do not share the same histologic features of remodeling.⁸⁹ The discrepancies between these studies are probably due to differences in the clinical severity and the treatment of asthmatic patients selected for the studies.

Proteases and protease inhibitors

MMPs selectively degrade ECM components. They have been implicated in angiogenesis and in smooth muscle hyperplasia.^{24,25} MMPs also play a crucial role in the trafficking of inflammatory and structural cells.^{90,91} Four subclasses of MMPs have been identified: collagenase, gelatinase, stromelysin, and membrane-type MMPs.

MMP-9 is the major MMP expressed in BAL fluid⁹² and bronchial mucosal biopsy specimens⁹³ obtained from patients with asthma. In healthy subjects, MMP-9 is co-secreted with tissue inhibitor metalloprotease-1 (TIMP-1) in one-to-one stoichiometry. In the BAL fluid or sputum of patients with untreated stable asthma, the

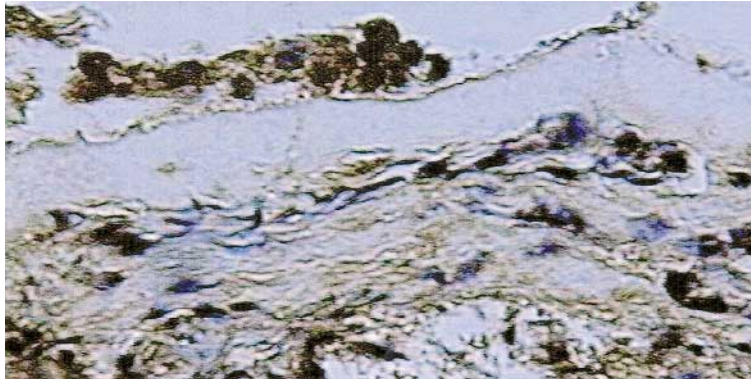


FIG 4. Immunoreactivity for fibronectin in a bronchial biopsy specimen obtained from an asthmatic subject (original magnification $\times 160$).

TIMP-1/MMP-9 molar ratio was greater than that in control subjects or patients with asthma receiving inhaled corticosteroids^{92,94} and was negatively correlated with FEV₁ values.⁹⁴ Thus an overproduction of TIMP-1 over MMP-9 seems to be a characteristic of patients with stable asthma. Moreover, no activated form of MMP-9 could be detected in BAL fluid from patients with untreated stable asthma, suggesting that there was enough counter-inhibitor (TIMP-1) to protect the molecule against activation.⁹² However, an excess of MMP-9 is found in BAL fluid from patients with uncontrolled asthma, or during a severe exacerbation,⁹⁵ suggesting that in these patients with unstable asthma, free metalloproteinolytic activity can be observed in the BAL fluid.

In asthma, MMP-9 may be secreted by macrophages,^{92,96} neutrophils,⁹⁵ eosinophils,⁹⁷ and epithelial cells,⁹⁵ but apparently not by basophils.

Imbalances between MMPs and their inhibitors may contribute to tissue damage and some of the remodeling features seen in asthma. MMP-9 can degrade native type IV and type V collagen, denatured collagen, entactin, proteoglycans, and elastin.⁹⁸ As such, MMP-9 has been shown to play a role in the disruption of the basement membrane and in the diapedesis of monocytes/macrophages or eosinophils to inflammatory foci by increasing the migration of these cells through the basement membrane. On the other hand, an excess of TIMP-1 over MMP-9 in stable asthma may protect the bronchi against metalloproteinase degrading activity.⁹⁹ However, this may interfere with cell trafficking and tissue repair and may also contribute to an increased ECM deposition and to fibrosis by its inhibition of MMP-9 or other MMPs *in vivo* (Fig 3).

Other proteases and inhibitors are released in the airways. In particular, free elastase was found to be increased in sputum of patients with asthma, and there was a correlation between its levels and low FEV₁ values.⁹⁴ The imbalance between elastase and $\alpha 1$ -proteinase inhibitor may play an important role in the degradation of ECM components and elastic fibers, as well as in the severity of asthma. Neutrophil elastase can reproduce many of the pathologic features of asthma and chronic

bronchitis including mucous gland hyperplasia,¹⁰⁰ excess mucus secretion, epithelial damage,¹⁰¹ and connective tissue destruction. In addition, neutrophil elastase can promote neutrophil recruitment in the lungs by inducing IL-8 production.¹⁰² Moreover, elastase exposure has been found to increase directed fibroblast migration through the ECM, a phenomenon that may play a role in the development of subepithelial fibrosis seen in inflammatory airway diseases such as asthma.¹⁰³ Finally, increased levels of active elastase may lead to the disruption of the elastic fiber network of the bronchi, resulting in the loss of a uniform intrapulmonary tension, which is crucial for the distribution of the inspired air evenly throughout the lungs, because radial traction on the walls of the small airways and alveoli is required to maintain their patency during inflation and deflation phases of ventilation (Fig 3).

Blood vessels

An increase in blood vessel area has been reported as part of the structural alterations observed in asthma,¹⁰⁴⁻¹⁰⁶ but the extent of neovascularization or angiogenesis is still unclear. Vascular endothelial growth factor levels are not increased in asthmatic airways, suggesting a low degree of angiogenesis in patients with stable asthma.¹⁰⁷

Smooth muscle

Hypertrophy and hyperplasia of airway smooth muscle¹⁰⁸⁻¹¹¹ have been reported in postmortem specimens of asthmatic bronchi. In some patients the muscle may occupy up to 20% of the bronchial wall thickness. This increase in muscle mass is also more important than in chronic bronchitis.¹⁰⁹ However, the importance of these findings is not completely clear, because a study in asthmatic patients who died of other causes did not reveal any hyperplasia or hypertrophy.

More recent studies have pointed out some degree of heterogeneity of the smooth muscle thickening.^{112,113} In patients who died of an asthma exacerbation, the increase in smooth muscle is far greater than in those who died of another cause.¹¹⁰ *In vivo* animal studies confirm that prolonged allergen exposure can increase smooth muscle thickness.¹¹⁴

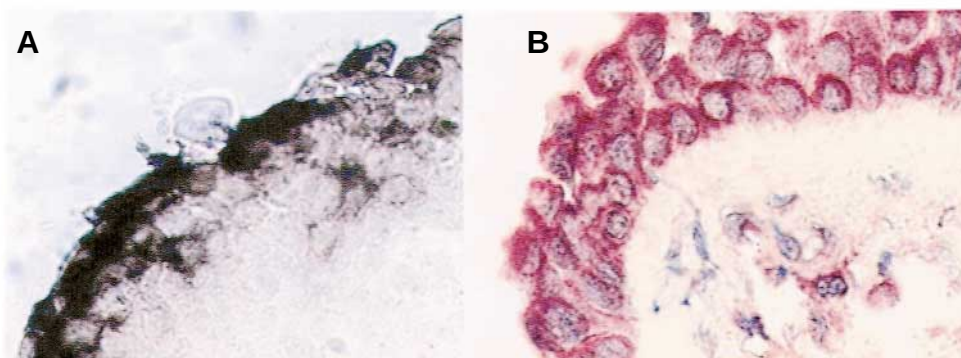


FIG 5. Expression of TGF- β in bronchial epithelial cells obtained from an asthmatic subject. **A**, In situ hybridization for TGF- β messenger RNA performed by using a digoxigenin-labeled probe and developed with nitroblue tetrazolium-5-bromo-4-chloro-3-inodoyl phosphate (positive staining is dark brown). **B**, Immunoreactivity for TGF- β protein (red staining) is expressed by both epithelial and submucosal cells (original magnification $\times 200$).

Mucous glands

Mucous glands are distributed throughout the airways in patients with asthma and are even present in peripheral bronchioles where they are normally absent. The mucous glands in the segmental bronchi of patients with asthma are considerably enlarged, and Dunhill et al¹⁰⁸ showed that their volume was twice as great in patients with asthma in comparison with healthy subjects. These values overlap those found in the case of chronic bronchitis. In asthma, hypertrophy of mucous glands appears to be the cause of increased volume, whereas hyperplasia of the mucus-secreting cells is usually observed in chronic bronchitis. However, animal models indicate that goblet cell hyperplasia and increased mucus production can occur in the large airways after prolonged allergen exposure, suggesting that a persistent inhalation of allergens may be an important causative factor for the development of mucous gland remodeling.¹¹⁴

CLINICAL CONSEQUENCES OF AIRWAY REMODELING IN ASTHMA

The pathophysiologic consequences of the aforementioned structural airway changes remain to be fully established. As already mentioned, the various components of the ECM have a range of biologic effects. Changes in the composition of the ECM could therefore profoundly influence the characteristics of airway inflammation in asthma. In addition, airway remodeling could have an important effect on lung function. This latter aspect has been most extensively investigated to date.

Non-specific bronchial hyperresponsiveness

Non-specific bronchial hyperresponsiveness (BHR) is the major functional abnormality in asthma.^{115,116} Convincing mathematical models suggest that remodeling, which results in an increased thickness of the airway wall, thickening of the smooth muscle layer, and changes in the adventitial matrix, significantly contributes to BHR.¹¹⁷ However, at the same time, other models predict

TABLE I. Potential effect of remodeling on bronchial responsiveness

Increased non-specific bronchial responsiveness
Thickening of airway wall ^{66,67}
Increased stiffness inner airway wall, affecting buckling pattern ¹¹⁹
Smooth muscle hypertrophy/hyperplasia ¹¹⁷
Loss of elastic recoil on contracting smooth muscle ¹²⁰
Increased random peripheral airway closure ¹²¹
Protection against exaggerated airway narrowing
Increased preload on contracting smooth muscle ¹²²
Interference of ECM components with smooth muscle contraction ¹²³
Smooth muscle banding ¹²⁴

that remodeling could actually protect against excessive airway narrowing, thus opposing BHR (Table I).¹¹⁸⁻¹²⁴

Different mathematical models describe the potential effect of these structural changes on both aspects of BHR. According to Poiseuille's law for laminar flow, it was calculated that small changes in airway wall thickness, especially internal to the smooth muscle layer, which are insufficient to affect the resistance to airflow under basal conditions, will for the same degree of smooth muscle contraction lead to an exaggerated decrease in airway resistance, thus contributing to increased airway sensitivity.^{66,67} In humans, it has also been hypothesized that the vascular engorgement of these vessels and consequent thickening of the airway mucosa lead to narrowing of the lumen of the bronchi, an increase in airway resistance, and a decrease in forced expiratory flow rates.¹²⁵

Moreover, subepithelial collagen deposition could increase the stiffness of the inner layer of the airway wall in comparison with the surrounding submucosa. This phenomenon can lead to formation of a relatively small number of large mucosal folds instead of a large number of very thin folds when the airway buckles in response to smooth muscle contraction. The consequence is a larger increase in the intraluminal airway pressure in response to the same degree of smooth muscle contraction.¹¹⁹ Fac-

tors considered to cause enhanced maximal airway narrowing include an increase in the smooth muscle layer and changes in the structure of the adventitial ECM, which in combination with fluid fluxes during smooth muscle contraction lead to a loss of elastic parenchymal recoil on contracting airway smooth muscle.^{117,120}

Animal studies further illustrate the complexity of the whole process. Experiments in dogs confirm that increasing airway wall thickness by infusing saline solution potentiates airway reactivity to inhaled histamine.¹²⁶ In a rat model, characteristics of airway remodeling were induced by exposing animals repeatedly over prolonged time to aerosolized ovalbumin. This results in an increased thickness of the airway wall in both large and small airways associated with an increase in BHR. However, with a more prolonged exposure, scarring occurs with increased fibronectin and collagen deposition mainly in the outer airway wall and reduction in the thickness of the airway wall. At the same time, BHR wanes and even turns into a slight hyporesponsiveness.¹²⁷ These findings support the mathematically derived concepts relating airway responsiveness to wall thickness. However, at the same time, these observations also illustrate that depending on its location and extensiveness within the airway wall, remodeling may not be associated with BHR and may even protect against excessive airway narrowing.¹²² Increased collagen deposition within the airway wall around the smooth muscle layer also interferes with smooth muscle contraction, again limiting airway narrowing.¹²³ Similarly, increased collagen deposition around the smooth muscle layer could have the effect of banding. This has been shown to oppose thickening of smooth muscle cells during contraction, and hence to oppose maximal shortening of the smooth muscle layer.¹²⁴

In addition, although structural airway changes can profoundly influence BHR, alterations in smooth muscle behavior are another important determinant. Changes in smooth muscle shortening velocity could, for example, explain the reduced bronchodilating effect of inspiration in patients with asthma compared with healthy individuals.¹²⁸ Under normal conditions, traction exerted on the adventitial area of smooth muscle during deep inspiration will elongate smooth muscle, breaking rapid cycling cross-bridges between actin and myosin and thus reducing the tensile force of the muscle cells. Increased shortening velocity, rapidly re-establishing these cross-bridges, will largely inhibit this relaxing effect. Moreover, the force generated by smooth muscle cells depends on the cell length when the stimulus is applied. The same stimulus applied to a smooth muscle that has rapidly shortened induces far less strength than if applied to a muscle cell fixed at a shortened length. Importantly, these alterations in the dynamics of smooth muscle contraction or the force generated cannot be properly predicted on the basis of morphometric analysis or by assessing isometric contraction of smooth muscle preparations *in vitro*.¹²⁹⁻¹³¹ Indeed, it has been shown that sensitized airway smooth muscle displays increased shortening velocity, without any concomitant change in isometric force-generating capability.¹³²

Lack of airway distensibility and accelerated decline in FEV₁

Reversibility of airflow obstruction, either spontaneously or in response to treatment with β_2 -agonists and/or steroids, is a diagnostic feature of asthma. However, a complete normalization of FEV₁ cannot always be obtained.¹³³ Some reports have linked this phenomenon to severity of the disease, but irreversible airflow limitation has also been described in individuals without symptoms.¹²⁶ Furthermore, assessment of airway caliber by measurement of FEV₁ might underestimate the occurrence of this phenomenon because peripheral lung resistance can be increased even in patients with asymptomatic asthma and a normal FEV₁.¹³⁴

Asthma has also been associated with an accelerated decline in FEV₁, although the differences in comparison with non-asthmatic subjects are less marked than the decline in FEV₁ observed in smokers.¹³⁵⁻¹³⁷ Patients with asthma who smoke clearly have a greater decline in FEV₁ than non-smoking patients.¹³⁶

It has been proposed that these functional abnormalities are associated with airway remodeling.^{3,138,139} However, definite proof is difficult to obtain because of the impossibility of correlating these functional abnormalities with the pathology of the entire bronchial wall because endobronchial biopsy specimens reflect only part of the structural changes that can occur. Another potentially confounding factor relates to lung growth and development during childhood in patients with asthma. Lung growth is reduced in asthmatic children in proportion to the severity of asthma.¹⁴⁰ The maximal FEV₁ reached in adolescence is a determining factor in the subsequent evolution of FEV₁ throughout life.^{141,142} A striking observation is that the accelerated decline in FEV₁ seems to occur early in asthma and stabilizes to within a normal range throughout the evolution of the disease.^{136,143} This would mean that if lung function abnormalities were only due to remodeling, structural changes would occur early during the course of the disease with relatively few additional changes later in life. However, subepithelial fibrosis has been demonstrated in bronchial biopsy specimens of very young children, before the development of asthma symptoms.¹⁴⁴

Moreover, no correlation has been found between the degree of thickening of the reticular basement membrane and the duration of asthma⁷⁶ or baseline FEV₁ in adulthood.^{73,75,145}

It is also important to remember that the decline in FEV₁ shows a large degree of heterogeneity, for reasons that are as yet unknown.¹⁴⁶

Therefore the exact relationships between remodeling and functional abnormalities need to be further studied, but it appears that lung function abnormalities are not only due to remodeling.

RADIOGRAPHIC FINDINGS

High-resolution computed tomography (HRCT) scans provide indirect information about airway remodeling in

asthma. Anatomic pulmonary changes including bronchial wall thickening, emphysema, and bronchiectasis have been demonstrated by HRCT scan in many patients with asthma.¹⁴⁷⁻¹⁵¹ Bronchiectasis in asthma is usually not extensive and is rarely associated with clear-cut symptoms of sputum production. Asthma may therefore lead to physiologic features of chronic obstructive pulmonary disease but may be distinguished by a higher ratio of airway to parenchymal abnormalities on CT scan.¹⁵² These abnormalities, which show a remodeling of the airways, are more extensive in severe forms of asthma and in non-allergic rather than in allergic patients.¹⁴⁸ Patients having asthma with abnormal HRCT changes demonstrate poorer lung function and less hyperreactive bronchi than those without.¹⁵³

IMPLICATIONS FOR TREATMENT

Although the exact clinical relevance of airway remodeling is not completely clear, it is proposed that treatment or prevention of remodeling is a crucial element in asthma management.

β_2 -Agonists and CysLT antagonists have been shown to reduce smooth muscle proliferation *in vitro*.¹⁵⁴⁻¹⁵⁶ However, their effect on remodeling in asthma is largely unknown.

The role of inhaled corticosteroids in airway remodeling needs to be better assessed. The broad *in vitro* pharmacologic profile of corticosteroids makes it difficult to predict their overall effect on remodeling. It is likely that remodeling results from a repair process in response to persistent inflammation and inhibition of pro-inflammatory mediators, MMPs, cytokines, and growth factors by corticosteroids should prevent or reverse remodeling. On the other hand, inflammation is a self-limited process, and by preventing proper wound healing, MMP and growth factor production, corticosteroids may lead to the persistence of chronic inflammation, thus indirectly enhancing remodeling. In some models a pro-fibrogenic effect of corticosteroids has been demonstrated.^{157,158} To complicate issues even further, *in vitro* studies indicate that the effect of steroids differs depending on the cell type and possibly the activation state.⁹⁶

Currently available data indicate that despite these theoretical concerns, treatment with inhaled corticosteroids does not enhance tissue remodeling in established asthma. The thickness of the reticular basement membrane is usually unchanged or only slightly reduced.¹⁵⁹⁻¹⁶¹ In one study it has been shown that if the dose of inhaled corticosteroids is adapted according to the degree of BHR, a reduction in the reticular basement membrane pseudo-thickening can be achieved.¹⁶² In addition, high doses of inhaled corticosteroids significantly reduce airway vascularity.¹⁶³

These morphologic data correspond to the clinical observation that prolonged treatment with inhaled corticosteroids improves both hypersensitivity and hyperreactivity of the airways, thus suggesting an effect on components of remodeling.¹⁶⁴⁻¹⁶⁶ However, in most studies BHR improves, but does not return within normal limits,

suggesting that corticosteroids cannot fully reverse remodeling.¹⁶⁷

This raises the question of whether it would not be more beneficial to start inhaled corticosteroids at an early stage of asthma to prevent the inflammatory cascade, which in turn induces structural remodeling, instead of reversing established lesions. This hypothesis has been tested in a rat model^{168,169} in which pretreatment with fluticasone propionate reduces airway inflammation and also partly prevents goblet cell hyperplasia, fibronectin deposition, thickening of the airway wall, and the accompanying increase in BHR. However, treatment with fluticasone after allergen exposure, although preventing further progression of structural airway changes, does not reverse already established alterations.

This concept also seems to be supported in humans by a limited number of studies in children and adults, which would indicate that postponing treatment with steroids results in a loss of the maximal achievable improvement. The effect of inhaled corticosteroids on the natural course of asthma is still debated because of the lack of long-term prospective studies.¹⁷⁰⁻¹⁷⁶ Large clinical studies, including not only evaluation of efficacy but also side effects and a pharmaco-economical evaluation together with a better insight into the phenomena of remodeling, are needed to further address this important issue. In addition, the effects of other forms of controller medication and immunotherapy also remain to be examined.

CONCLUSION

Remodeling of the airways is a proven structural concept, but is remodeling of the airways a proven clinical concept? It is clear that changes in the ECM, smooth muscle, and mucous glands have the capacity to influence airway function and reactivity in asthma. However, it is not known how each of the many structural changes that occur in the airway wall contributes to altered airway function in asthma. In asthma, remodeling is almost always present in biopsy specimens (eg, collagen deposition on basement membrane) but is not always clinically demonstrated. Destruction and subsequent remodeling of the normal bronchial architecture are manifested by an accelerated decline in FEV₁ and BHR. This irreversible component of the airway obstruction is more prominent in patients with severe asthma and even persists after aggressive anti-inflammatory treatment. What is clear, however, is that patients with asthma, children or adults, are heterogeneous with regard to the clinical consequences of structural remodeling.

Airway remodeling appears to be of great importance for understanding the long-term follow-up of patients with asthma,¹⁷⁷ but there are major gaps in our knowledge. Physiologic correlations with pathology represent a major missing link, which should be filled. More long-term studies are needed to appreciate the prevention and treatment of remodeling. Future research should therefore provide better methods for limiting airway remodeling in asthma.

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