

Rostrum

Allergic rhinitis: A disease remodeling the upper airways?

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The nasal and bronchial mucosa present similarities and differences. Remodeling is defined as “model again or differently, reconstruct” and is present in the airways of most if not all asthmatic patients. Even though inflammation is similar in allergic rhinitis and asthma, the pathologic extent of nasal remodeling in patients with rhinitis seems to be far less extensive than that in the bronchi of asthmatic patients. Epithelial damage is only minimal, and the reticular basement membrane does not appear to be largely pseudothickened. Moreover, the demonstration of fibrogenic growth factors in the nasal mucosa of patients with allergic rhinitis is lacking because of the paucity of studies. The reasons why remodeling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still unclear, but 2 hypotheses can be put forward. On one hand, the cytokine production of smooth muscle cells might partly explain differences in remodeling of the 2 sites of the airways. On the other hand, the genes of the embryologic differentiation might persist in the nose and bronchi or might be re-expressed in asthma and rhinitis. Because the nose is of ectodermal origin and the bronchi of endodermal origin, these genes might also govern remodeling patterns. More studies are urgently required to better characterize nasal remodeling in patients with rhinitis. A better understanding of nasal and bronchial remodeling might help to identify new pathways and new therapeutic strategies to reduce long-term remodeling in asthma. (*J Allergy Clin Immunol* 2004;113:43-9.)

Key words: Asthma, rhinitis, remodeling, endoderm, ectoderm, smooth muscle

The nasal and bronchial mucosa present similarities, and epidemiologic studies have shown that rhinitis and asthma are commonly associated.^{1,2} However, the nose and bronchi have a different embryologic origin, smooth muscle is present only in the bronchi, and there are differences between rhinitis and asthma.

Abbreviations used

MMP: Matrix metalloproteinase
TGF: Transforming growth factor
TIMP: Tissue inhibitor of metalloproteinases

Remodeling is defined as “model again or differently, reconstruct.” Remodeling occurs usually in reaction to an inflammatory condition, which in turn leads to a normal reconstruction process (model again) or a pathologic process (model differently), and is not necessarily associated with fibrosis. Remodeling therefore exists in all inflammatory diseases, but its control differs largely depending on the disease.

In 1992, it was proposed that asthma, a chronic inflammatory disease, was associated with abnormal airways remodeling,³ and it took several years to begin to understand what the term “remodeling” meant.⁴⁻⁶ In allergic rhinitis, another chronic inflammatory disease, remodeling is still poorly understood. Even though inflammation is similar in allergic rhinitis and asthma, the pathologic extent of nasal remodeling, as well as its clinical consequences, might be different from those of bronchi.

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced after indoor or outdoor allergen exposure by an IgE-mediated inflammation of the membranes lining the nose.² Remodeling might differ in the nasal mucosa of patients with allergic rhinitis and nasal polyps, which will not be considered in this article because they are driven by different mechanisms.

EMBRYOLOGIC ORIGIN OF THE NOSE AND BRONCHI

The embryologic development of the upper and lower airways begins during the fourth week of gestation and continues for many years after birth. The nose develops from the nasal placode and the nasal prominences, with the larynx, trachea, bronchi, and lungs developing from the laryngotracheal groove in the ventral wall of the primitive pharynx (Fig 1).¹

During the fourth week, the embryo undergoes a complex process of embryonic folding.⁷ The process of midline fusion transforms the flat embryonic endoderm into a gut tube. The respiratory tree originates as a diverticulum of the endodermal foregut, which undergoes a controlled series of branching.⁸

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Supported by institutional funding: INSERM (France) and CNR (Italy). Received for publication July 21, 2003; revised September 9, 2003; accepted for publication September 18, 2003.

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doi:10.1016/j.jaci.2003.09.047

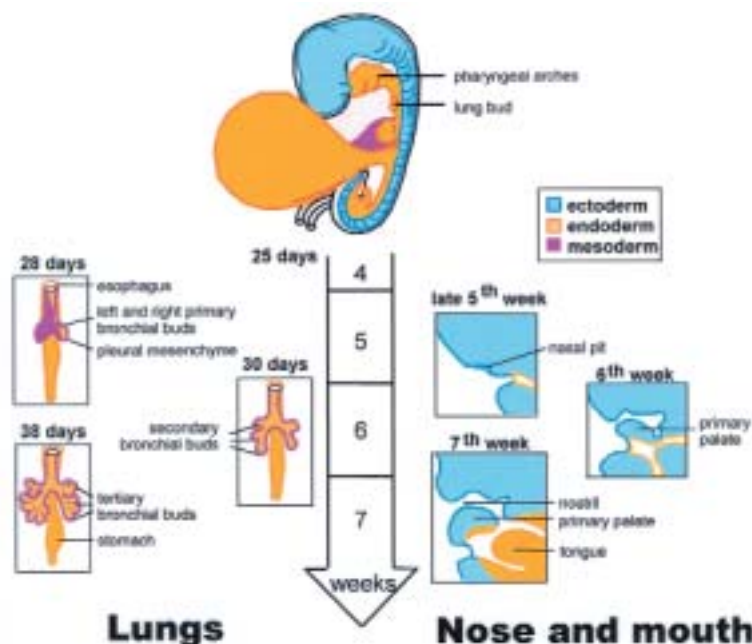


FIG 1. Embryologic origin of the airways.

The development of the face is a dynamic multistep process that starts with the formation of neural crest cells in the developing brain and their subsequent migration to form, together with mesodermal cells, the facial processes.⁹ A pair of thickened ectodermal nasal placodes develops during the fourth week of gestation.⁷ The center of each placode is invaginated to form the epithelium of the nasal passages, whereas the raised margin of the placode gives rise to the nose.¹⁰

SIMILARITIES AND DIFFERENCES OF THE NASAL AND BRONCHIAL MUCOSA IN ASTHMA AND RHINITIS

In healthy subjects the airways mucosa has a similar structure in the nose and bronchi. The pseudostratified epithelium with columnar ciliated cells is resting on a basement membrane. Underneath the epithelium, in the submucosa, vessels and mucous glands are present with structural cells (fibroblasts), some inflammatory cells, and nerves.¹¹⁻¹³

There are also differences. In the nose there is a large supply of subepithelial capillaries, arterial systems, and venous cavernous sinusoids. On the other hand, smooth muscle is present from the trachea to the bronchioles. The physiology of nasal and bronchial epithelial cells might differ in terms of their cohesion because cadherin expression differs in response to stimulation.^{14,15}

In asthma and rhinitis inflammation of the nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, including eosinophils, mast cells, T lymphocytes, and macrophages,^{4,16} and similar pro-inflammatory mediators (histamine and cysteinyl leukotrienes), T_H2 cytokines, and chemokines.^{17,18}

However, there are differences between both sites. The magnitude of inflammation might not be identical,¹⁹ and eosinophilic inflammation of the nose exists in asthmatic patients with or without nasal symptoms.²⁰

BRONCHIAL REMODELING IN ASTHMA AND RHINITIS

Features of remodeling in asthma

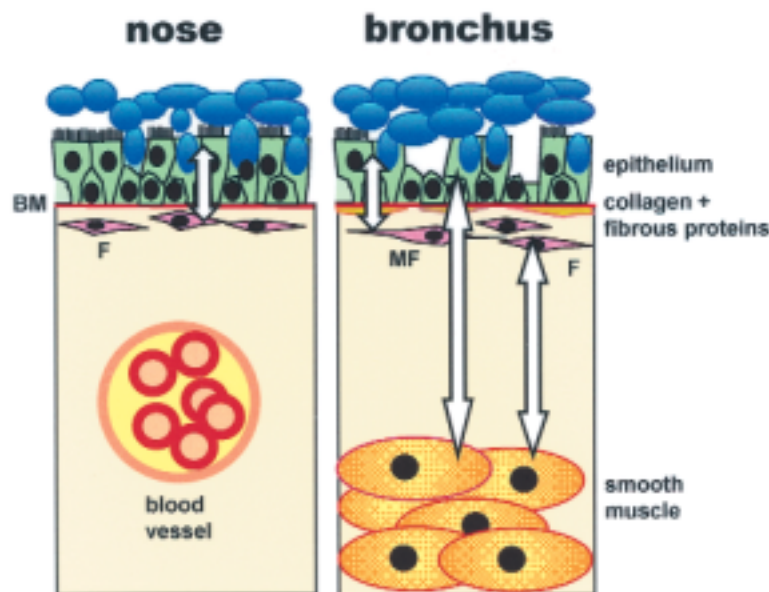
In asthma tissue modeling and remodeling coexist in a dynamic process (Table I).^{4,21-23}

There are also cellular and molecular criteria involved in remodeling, including increased expression and release of growth factors (transforming growth factor [TGF]- β , epidermal growth factor,²⁴ fibroblast growth factor,²⁵ collagen and fibronectin deposition beneath the basement membrane, increased levels of elastase,²⁶ metalloproteinases, and tissue inhibitors of metalloproteinases [TIMP]²⁷) in airway fluids. The role of ADAM 33 (a disintegrin and metalloproteinase domain 33) is still under careful examination.²⁸

Reticular basement membrane thickening is already present in children with difficult asthma and to a similar extent as that seen in adults with asthma.²⁹ Postmortem and biopsy studies on children with asthma show an increase in the size of mucous glands but not in smooth muscle.³⁰ Thus an important question is whether remodeling of the airway wall precedes asthma³¹ and whether airways remodeling is in fact associated with the persistence of fetal processes³² or their reactivation.²¹

Features of bronchial remodeling in rhinitis

Few studies have examined features of bronchial remodeling in rhinitis. The size of the reticular basement mem-



BM: basement membrane, F: fibroblast, MF: myofibroblast

FIG 2. Epithelial-mesenchymal interactions in the nasal and bronchial mucosa.

TABLE I. Inflammatory and remodeling patterns in the nasal and bronchial mucosa in nonsmoking subjects

		Nasal mucosa, rhinitis-asthma	Bronchial mucosa, asthma
Epithelium	Shedding	Variable, often minimal	Common, particularly in severe disease
Basement membrane	Metaplasia	Sometimes	Very rarely
	Collagen IV	Normal	Normal
	Collagen III, V, fibrous proteins	Pseudothickening might occur, although limited	Pseudothickening very common
Submucosa	Eosinophils	Often present	Often present
	CD4 ⁺ T cells	Commonly increased	Commonly increased
	CD8 ⁺ T cells	Low numbers	Low numbers
	Elastase-positive cells	Sometimes increased numbers	Usually low numbers
	CD68 ⁺ cells	Sometimes increased numbers	Often increased numbers
	Collagen deposition	Possible	Common but not extensive
	Fibroblasts	Possibly increased numbers	Increased numbers
	Myofibroblasts	?	Present
	Smooth muscle	None	Metaplasia and hyperplasia

brane is increased in nonasthmatic subjects with atopy³³ and in patients with allergic rhinitis.^{34,35} In sputum, patients with mild asthma have higher eosinophil counts and higher eosinophil cationic protein and tryptase levels than patients with rhinitis who have higher eosinophil counts than healthy control subjects.³⁶ These data suggest that patients with rhinitis have some remodeling features that are, however, not as extensive as in asthma³⁷ (Fig 2).

AIRWAY REMODELING IN ALLERGIC RHINITIS

Epithelium

Only a few studies have been performed to investigate the epithelium in the nasal mucosa of patients with allergic rhinitis, and contradictory results have been

observed.³⁸ By using light and electron microscopy, epithelial damage and torn tight junctions of the epithelial cells were found in the nasal mucosa of patients with allergic rhinitis.³⁹

Outside of the pollen season, patients with seasonal allergic rhinitis have a thicker epithelium than normal subjects.⁴⁰ During pollen exposure, allergic patients present a marked goblet cell hyperplasia, whereas metaplasia and ciliated cell dysplasia were found throughout the year.⁴¹ In another study in patients with seasonal allergic rhinitis, no significant differences were found in the numbers of goblet cells before and during the season.⁴²

Patients with perennial rhinitis have an epithelium thickness comparable with that of normal subjects.^{40,43} In subjects allergic to house dust mites, nasal epithelial

damage was found in the anterior nasal mucosa, in which nonciliated cells were prevalent but minor in the posterior nasal mucosa.⁴⁴ The alteration of the epithelium is far less extensive in the nose than in the bronchi of the same asthmatic patients.¹⁹ Epithelial cell metaplasia has been observed in nasal biopsy specimens of some patients with perennial rhinitis.⁴⁵⁻⁴⁷ Moreover, episialin expression differs in the nasal and bronchial epithelium.¹⁹ Long-term treatment with intranasal corticosteroids reduces metaplasia.⁴⁷

Taking all the studies together, it appears that epithelial disruption and desquamation is a feature of bronchial epithelium in asthma but is less marked in the nasal epithelium of patients with rhinitis. It could be argued that bronchial epithelial shedding in asthma might be due to an artifact during the biopsy procedure. This might only be partly true for several reasons. First, epithelial shedding is more extensive in patients with moderate persistent asthma than in patients with mild intermittent asthma.⁴⁸ Second, when bronchial and nasal biopsy specimens were carried out in the same asthmatic patients by using the same forceps, epithelial shedding was far greater in the bronchi than in the nose.¹⁹ However, it might be argued in this study that it is easier to perform nasal biopsies than bronchial biopsies and that increased shedding in the bronchial mucosa is still an artifact. Third, in the same study, by using a marker of epithelial cohesion, episialin,⁴⁹ it was shown that its immunoreactivity was altered in bronchial but not in nasal biopsy specimens of the same patients.¹⁹ It is therefore strongly suggested that shedding, or at least epithelial fragility, is far greater in the bronchial mucosa of asthmatic patients than in the nasal mucosa of patients with allergic rhinitis, even though the nasal mucosa is more exposed to noxious agents and allergens than the bronchial mucosa.

Reticular basement membrane

In the nasal and bronchial biopsy specimens obtained from the same untreated patients with moderate asthma, the thickness of the reticular basement layer was increased by comparison with that in control subjects, but it was significantly greater in the bronchial mucosa than in the nasal mucosa.¹⁹ However, few studies have examined the nasal reticular basement membrane with electron microscopy⁵⁰ or immunohistochemistry,⁵¹ and results are not consistent. In a study there was no significant difference in the total amount of collagen between allergic and nonallergic subjects.⁵⁰ In another study,⁵² although there was no obvious change in localization of the 3 types of collagen, extensive immunoreactivity for type I and III collagen was observed in allergic subjects at the subepithelial basement membrane zone. The thickness of the basement membrane zone, which corresponds to regions positive for type I and III collagen antibodies, was greater in allergic subjects than in nonallergic subjects.

It therefore seems that in allergic rhinitis there is some pseudothickening of the reticular basement membrane caused by collagen and fibrous protein deposition but to a lesser extent than in asthma.

Fibroblasts and growth factors

There is no histologic study on fibroblasts in allergic rhinitis. By comparison with control subjects, in patients with allergic rhinitis, there is a low expression of TGF- β ; an expression of TGF- α in the basement membrane and extracellular matrix, including lymphatic, vascular, and glandular structures⁵³; and an increased nerve growth factor immunoreactivity.⁵⁴⁻⁵⁶ Epidermal growth factor levels did not differ between patients with allergic rhinitis and control subjects.⁵⁷

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are major proteolytic enzymes that are involved in extracellular matrix turnover.⁵⁸ MMP-9 is not increased in perennial allergic rhinitis,⁵⁹ but 3 to 10 hours after nasal allergen challenge, a parallel increase in eosinophil cationic protein and MMP-9 was observed.⁶⁰ Large amounts of TIMP-1 and TIMP-2 mRNA and protein were found in the nasal mucosa of patients with perennial rhinitis.⁵⁹

Blood vessels

The stereologic estimation of blood vessel surface and volume densities were studied in human normal and rhinitic nasal mucosa. By comparison with controls subjects, the volume and surface densities of the cavernous blood vessels in patients with rhinitis were unaltered, and there was no evidence of vascular remodeling.⁶¹ In another study the hypervascularity and overexpression of the platelet-derived endothelial cell growth factor, an angiogenic factor, were found in allergic nasal mucosa.⁶²

Conclusions

Airways remodeling exists in rhinitis, but it seems to be far less extensive than in asthma. Even though the epithelial mesenchymal trophic unit exists in rhinitis,⁶³ epithelial damage is only minimal, and the reticular basement membrane does not appear to be largely pseudothickened. Moreover, the demonstration of fibrogenic growth factors in the nasal mucosa of patients with allergic rhinitis is lacking because of the paucity of studies. It is therefore clear that more studies are required to fully appreciate remodeling in rhinitis, but from the existing data, it is obvious that there are major differences between asthma and rhinitis.

IMPORTANCE OF THE SMOOTH MUSCLE IN THE EPITHELIAL-MESENCHYMAL TROPHIC UNIT IN BRONCHIAL REMODELING

The epithelial-mesenchymal unit recently delineated²¹ is of cardinal importance in asthma, but this concept has reduced the importance of the smooth muscle as an inflammatory and regulatory cell.⁶⁴⁻⁶⁶ However, it is possible that some of the differences in remodeling between the nasal and bronchial mucosa are related to the smooth muscle cells interacting with the epithelium and other mesenchymal cells.⁶⁷⁻⁶⁹ Thus increased epithelial shed-

ding, basement membrane pseudofibrosis, and other features of airway remodeling, which are more common in asthma than in rhinitis, might be associated with the secretory activity by the smooth muscle. On the other hand, smooth muscle cells are modulated by mediators and cytokines released from other neighbouring structural, inflammatory, or epithelial cells, with a cross-talk between all these cells (Fig 2).

Bronchial epithelial activation and shedding in asthma increases the contractile response of bronchial smooth muscle. In response to mechanical stresses similar to those occurring in vivo during airway constriction, bronchial epithelial cells increase the release of fibrogenic mediators, such as TGF- β and endothelin.⁷⁰

EMBRYOLOGIC DIFFERENCES BETWEEN THE BRONCHI AND THE NOSE MIGHT EXPLAIN THE DIFFERENCES IN REMODELING

The early occurrence of allergic asthma suggests that prenatal influences are of importance.⁷¹ It is likely that defects in early development of the lung, as well as the immune system, are involved in the pathogenesis of asthma. There are several features of the developing lung that are present in asthma, such as an enhanced expression of tenascin⁷² or the development of myofibroblasts.⁷³ In the developing lung, the induction of smooth muscle differentiation is closely related to branching morphogenesis.⁷⁴

Many of the genes involved in IgE synthesis and airways (re)modeling might be conserved fetal genes⁷⁵ that might not be silenced during early infancy. We hypothesized that their gene products might play an important role in the induction and maintenance of the pathogenesis of asthma.³² Because the nose and bronchi have different embryologic origins, it might be proposed that the persistence of fetal genes is involved in the differences observed between the remodeling of the nose and the bronchi. However, this hypothesis is not supported by any study.

CONCLUSIONS

Modeling and remodeling are always present in inflamed tissues, and it is not surprising that they exist in the nasal and bronchial mucosa of patients with allergic rhinitis and asthma. However, differences exist, and it appears that remodeling in the nose is less extensive than that in the lungs. However, more studies are urgently needed to characterize modeling and remodeling of the nasal mucosa.

The reasons why remodeling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still unclear, but 2 hypotheses can be put forward. On one hand, the secretory activity of smooth muscle cells might partly explain differences in remodeling of the 2 sites of the airways. On the other hand, the genes of the embryologic differentiation might persist in the nose and bronchi or might be re-expressed in asthma and rhinitis. Because the embryologic origins of the nose and bronchi differ, these genes might also govern remodeling pat-

terns. A better understanding might help to identify new pathways and new therapeutic strategies to reduce long-term remodeling in asthma.

RESEARCH NEEDS

Although nasal remodeling appears to differ from bronchial remodeling, there are many gaps in our knowledge that require further research. These include the following:

- a more extensive study of nasal and bronchial epithelium in the same asthmatic patients with disease of different severity and cause (including toluene 2,4-diisocyanate-induced asthma);
- the study of the cohesion of epithelial cells in the nose and bronchi of asthmatic patients and patients with rhinitis by using imaging techniques and immunohistochemistry;
- the study of mucous glands, the phenotype of mucous cells and MUC gene expression in the nose and bronchi of patients with allergic and nonallergic asthma;
- the characterization of fibroblasts and myofibroblasts in the nose and bronchi;
- the deposition of collagen, other fibrinous proteins, and proteoglycans in the submucosa of the nose and bronchi;
- the expression of growth factors in the submucosa of the nose and bronchi; and
- the comparison of remodeling patterns in the nasal mucosa of patients with rhinitis and nasal polyps.

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