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Remodeling in asthma

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Activity Objectives

1. To describe the different morphological changes that the airway epithelium undergoes during asthma.
2. To understand the different inflammatory mechanisms that contribute to airway remodeling.
3. To define the roles that viruses and tobacco use contribute to airway remodeling.
4. To describe the natural history of airway remodeling and possible therapeutic interventions.

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Airway remodeling encompasses the structural alterations in asthmatic compared with normal airways. Airway remodeling in asthmatic patients involves a wide array of pathophysiologic features, including epithelial changes, increased smooth muscle mass, increased numbers of activated fibroblasts/myofibroblasts, subepithelial fibrosis, and vascular changes. Multiple cytokines, chemokines, and growth factors released from both inflammatory and structural cells in the airway tissue create a complex signaling environment that drives these structural changes. However, recent investigations have changed our understanding of asthma from a purely inflammatory disease to a disease in which both inflammatory and structural components are equally involved. Several reports have suggested that asthma primarily develops because of serious defects in the epithelial layer that allow environmental allergens, microorganisms, and toxins greater access to the airway tissue and that can also stimulate the release of mediators from the epithelium, thus contributing to tissue remodeling. Lung-resident fibroblasts and smooth muscle cells have also been implicated in the pathogenesis of airway remodeling. Remodeling is assumed to result in persistent airflow limitation, a decrease in lung function, and airway hyperresponsiveness. Asthmatic subjects experience an accelerated decrease in lung function compared with healthy subjects, which is proportionally related to the duration and severity of their disease. (J Allergy Clin Immunol 2011;128:451-62.)

Key words: *Asthma, remodeling, airway smooth muscle, fibrosis, corticosteroid*

Airway remodeling encompasses alterations in structural cells and tissues in asthmatic as opposed to healthy airways. This was first described more than 85 years ago by Huber and Koessler[1] in their classic description of fatal asthma. However, it was not until recently that these alterations were found to contribute to the pathogenesis of asthma. Asthma was previously presumed to develop as the result of abnormal contraction of airway smooth muscle (ASM; bronchospasm) caused by an intrinsic abnormality in airway myocytes. The central role of inflammation in the pathogenesis of asthma was proposed after numerous reports demonstrating the influx of various inflammatory cells and mediators within bronchial biopsy specimens obtained from patients with

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Terms in boldface and italics are defined in the glossary on page 452.

Abbreviations used
AHR: Airway hyperresponsiveness
ASM: Airway smooth muscle
CAM: Cellular adhesion molecule
CT: Computed tomography
ECM: Extracellular matrix
ICAM-1: Intercellular adhesion molecule 1
ICS: Inhaled corticosteroid
MMP: Matrix metalloproteinase
TIMP: Tissue inhibitor of metalloproteinase
VCAM-1: Vascular cell adhesion molecule 1
VEGF: Vascular endothelial growth factor

varying disease severity.[2-4] Moreover, the beneficial clinical effect of steroids has confirmed the key role inflammation plays in the pathogenesis of asthma. Although these reports have set the groundwork for the "inflammation theory" of asthma, airway structural alterations revealed by various groups[5-9] have added more complexity to the understanding of the development of asthma. These alterations have been shown to contribute to the symptoms and physiologic abnormalities seen in asthmatic patients. It is now believed that chronic inflammation drives the remodeling response, leading to structural alterations responsible for the pathogenesis and clinical manifestations of asthma.

TISSUE REMODELING

Remodeling in general

Tissue remodeling refers to modifications to the normal composition and structural organization of tissues, which usually occur in response to various mechanical or physiologic forms of stress. Remodeling occurs in a wide range of tissues and organs, including the skin,[10] blood vessels,[11] heart,[12] gastrointestinal tract,[13,14] airways, and lung, and can be observed in almost all tissues susceptible to chronic injury, inflammation, or both.

Airway remodeling

Airway remodeling occurs in patients with several pulmonary disorders, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, and systemic sclerosis. In patients with these diseases, inflammatory conditions are associated with cellular and structural changes that result in thickening of the airway wall, thereby leading to airway narrowing and airflow limitation. Whereas remodeling in patients with chronic obstructive pulmonary disease involves structural changes to the small airways and remodeling in patients with cystic fibrosis is characterized by fibrotic, glandular, muscular, and vascular changes throughout the lung, airway remodeling in patients with asthma involves a wide array of pathophysiologic features, including epithelial changes, increased smooth muscle mass, increased numbers of activated fibroblasts/myofibroblasts, subepithelial fibrosis, and vascular changes primarily around the large airways. However, an important involvement of the small airways in the pathogenesis of asthma has been described.

HISTOPATHOLOGIC FEATURES OF REMODELING IN ASTHMATIC PATIENTS

Epithelial alterations

Morphologic changes to the airway epithelium are a key feature of airway remodeling in asthmatic patients. Epithelial alterations in asthmatic patients include shedding of the epithelium, loss of ciliated cells (Fig 1, *A* and *B*, white arrows), goblet cell hyperplasia, and upregulation of growth factors, cytokines, and ***chemokines***.[15-19] Many reports have also suggested that the barrier function of the airway epithelium in asthmatic patients is dysfunctional, exhibiting a breakdown in epithelial ***tight junction*** integrity along with impaired repair after injury.[20,21] However, it is important to note that epithelial changes are not a characteristic feature only of asthma and can be observed in patients with various pathologic conditions of the lung.

GLOSSARY

ADVENTITIA: The outer layer of the airway.

CHEMOKINE: Chemokines are the largest family of cytokines. They act by binding to G protein–coupled receptors. Their function in the immune system is to coordinate leukocyte trafficking and activation.

CYSTEINYL LEUKOTRIENES: A specific group of eicosanoids generated from lipoxygenases involved in allergic inflammation.

DENDRITIC CELLS: Hematopoietic cells that function as antigen-presenting cells for lymphocytes. Their name is derived from their multiple, thin membranous projections.

EICOSANOIDS: A class of lipids derived from polyunsaturated fatty acids (eg, arachidonic acid) that mediate inflammation.

ELASTIN: A protein similar to collagen that is the major component of elastic fibers. It is degraded by elastase from neutrophils.

IL-6: A cytokine that promotes T_H17 immune deviation, induces differentiation of mature B lymphocytes into plasma cells, and acts through signal transducer and activator of transcription 3 to produce its effects.

MATRIX METALLOPROTEINASES (MMPS): Proteases produced by the airway epithelium and inflammatory cells that are involved in degrading the extracellular matrix and tissue repair. They are induced by proinflammatory cytokines, and their levels are increased in the bronchoalveolar lavage fluid of asthmatic patients.

MUCUS: A substance lining membranes that functions to preserve the membranes, to act as a barrier, and to transport trapped material (in conjunction with cilia). Normal airway mucus is 90% water, and the remaining 10% is composed of protein, carbohydrate, and lipid. Mucin is a glycoprotein constituent of mucus.

OPTICAL COHERENCE TOMOGRAPHY: A new bronchoscopic imaging technique that has higher spatial resolution than computed tomography and does not involve ionizing radiation.

REACTIVE OXYGEN SPECIES (ROS): Substances typically generated at a low frequency during oxidative phosphorylation in the mitochondria and in a variety of other cellular reactions. ROS are capable of exerting cellular damage by reacting with intracellular constituents, such as DNA and membrane lipids.

TIGHT JUNCTION: A dynamic network of proteins that help seal the apical space between epithelial cells and regulate epithelial permeability. Proteins that are found in the tight junction can include junctional adhesion molecule 1, occludin, and claudins. The cysteine and serine protease components of the house dust mite allergen (Der p 1) can cleave junctional proteins.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF): The dominant growth factor controlling angiogenesis. Anti-VEGF neutralizing antibodies are used in cancer therapy.

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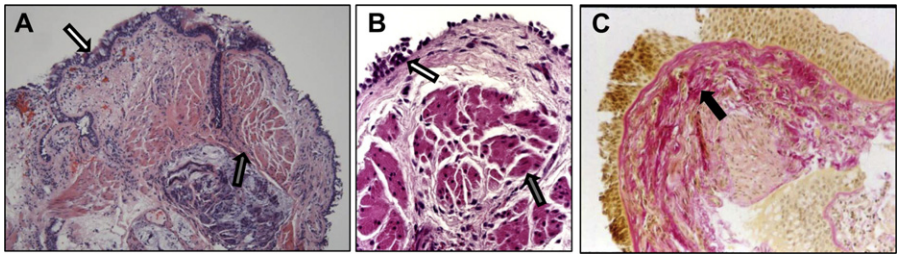

FIG 1. Histopathology of severe asthma. **A** and **B**, Bronchial biopsy specimens stained with hematoxylin and eosin at low magnification (Fig 1, *A*) and higher magnification (Fig 1, *B*) demonstrate structural alterations of the airway wall in asthma, including epithelial shedding *(white arrows)* and increased airway smooth muscle mass *(gray arrows)*. **C**, Severe asthma is also associated with increased subepithelial collagen deposition (red stain; *black arrow*).

Mucus secretion and goblet cells

Mucus hypersecretion of the mucins MUC5AC and MUC5B by goblet cells is a pathophysiologic feature of airway remodeling in asthmatic patients.[22] The origin of these goblet cells is not well understood, although Clara cells and ciliated cells have been implicated as goblet cell progenitors.[22] T_H2 cytokines (predominantly IL-9 and IL-13), as well as IL-1β, TNF-α, and COX-2 and their associated intracellular signaling pathways, have been shown to be involved in the upregulation of mucin synthesis and the development of goblet cell hyperplasia.

Subepithelial fibrosis

Fibroblasts are large, flat stellate cells that reside in close proximity to the basal epithelium. In an inflammatory environment such as the asthmatic airway, fibroblasts are activated/differentiated into myofibroblasts, which secrete proinflammatory mediators and extracellular matrix (ECM) proteins, including collagens I, III, and V; fibronectin; tenascin; lumican; and biglycan.[23-26] The ECM compartment of the airway wall is dynamic, reflecting the net balance of synthesis and degradation that is regulated by the actions of ***matrix metalloproteinases*** (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[27] However, a shift in this balance toward increased matrix deposition results in fibrosis, leading to altered structure and abnormal mechanical properties. In asthmatic patients susceptibility to injury and aberrant repair responses result in persistent activation of fibroblasts, leading to subepithelial fibrosis (Fig 1, *C*, black arrow).[28]

Increased smooth muscle mass

ASM cells constitute the main structural cells within the bronchi, and the remodeling of ASM is considered to be the primary cause of airway obstruction (Fig 1, *A* and *B*, gray arrows). This is because in asthmatic airways ASM mass significantly increases because of ASM cell proliferation (hyperplasia) and increased cell size (hypertrophy). Additionally, the migration of ASM cells toward the epithelium is a contributing factor. In addition to structural changes, ASM cells participate in the inflammatory and remodeling process through the expression of cellular adhesion molecules (CAMs), receptors for cytokines (eg, TNF-α), chemokines (RANTES, eotaxin, macrophage inflammatory protein 1α, and IL-8), and Toll-like receptors.[29,30] A wide range of inflammatory mediators, such as TNF-α, IL-1β, and IFN-γ, have been shown to induce the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on cultured ASM cells.[31] The surface expression of CAMs by ASM cells might be pivotal in regulating interactions with a variety of inflammatory cells, including eosinophils and T cells.[31,32]

Angiogenesis

Accumulating evidence has indicated an abnormal increase in the number and size of microvessels within bronchial tissue in remodeled airways.[33] This has been observed mainly below the basal lamina in the space between the muscle layer and the surrounding parenchyma. An imbalance between ***vascular endothelial growth factor*** (VEGF) and angiopoietin-1 has been shown to be involved in these abnormalities.[34] In fact, VEGF acts by increasing the permeability of these abnormal blood vessels,[35] resulting in vessel dilation and edema, which contribute to airway narrowing. In addition to providing nutrition to the airways, these vessels are the source of inflammatory cells and plasma-derived mediators and cytokines.[33]

MECHANISMS OF AIRWAY REMODELING

Inflammation

Inflammation is believed to be the driving force behind most features of airway remodeling (Fig 2). Multiple cytokines, chemokines, and growth factors released from both inflammatory and structural cells in the airway tissue create a complex signaling environment that drives airway remodeling. It is now believed that IgE and mast cells are implicated in the acute response and eosinophils and their highly basic granule-associated proteins in the late response, with T-cells, particularly T_H2 cells, orchestrating these responses through the production of cytokines, such as IL-4, IL-5, IL-9, and IL-13.[36-39] In asthmatic patients airway inflammation usually involves T_H2 cells, which are thought to modulate the inflammatory response through the release of T_H2 cytokines that are essential for IgE synthesis, chemokine production, airway eosinophilia, smooth muscle hyperplasia, and mucus production.[40-42] Although T_H2 cells are central to the pathogenesis of mild-to-moderate asthma, as the disease becomes more severe and chronic, T_H1 cells begin to play a role, possibly by mediating a regulatory function in patients with allergic asthma through the secretion of IFN-γ, which inhibits T_H2 cell proliferation.[42]

Recently, a third subset of effector T_H cells has been identified in patients with severe asthma that exclusively produces IL-17 cytokines (T_H17 cells).[43-45] The involvement of T_H17 responses in the pathogenesis of asthma has been shown by the overexpression of *IL17* mRNA in the airways in a murine asthma model.[46] This was confirmed by Al-Ramli et al,[47] who showed that IL-17

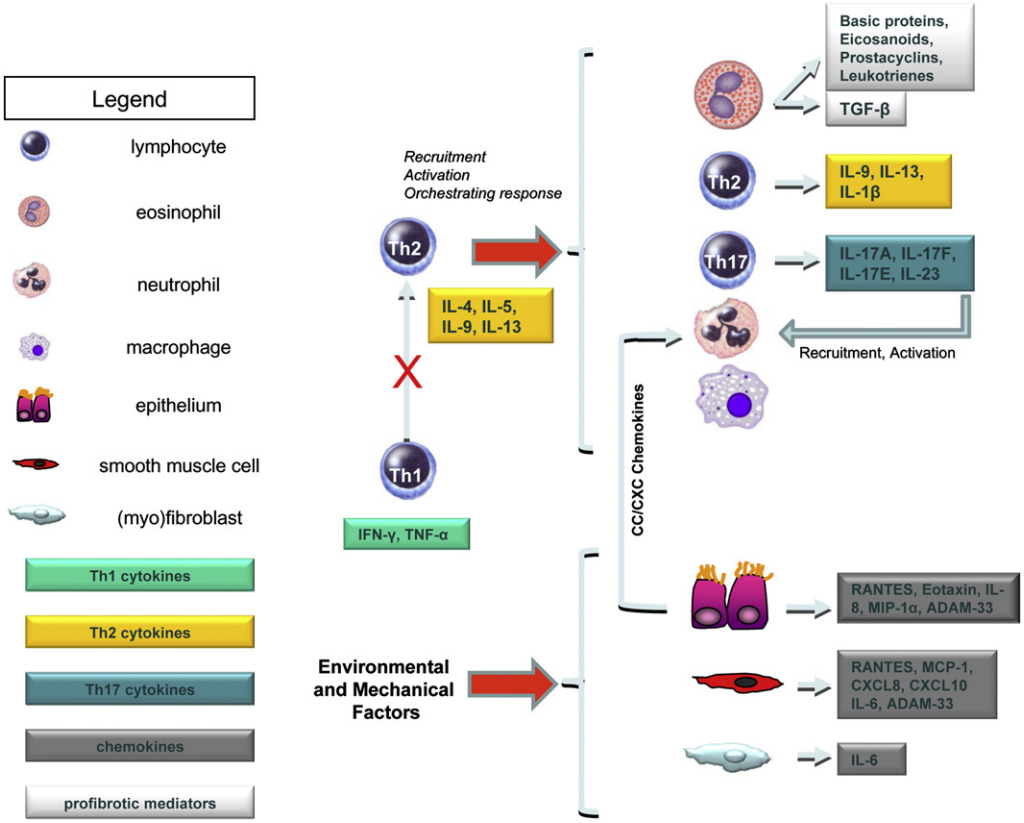

FIG 2. Inflammatory mediators and cell types involved in the pathogenesis of airway remodeling in asthmatic patients. Asthma-associated inflammation primarily involves T_H2 and T_H17 pathways. *MCP-1*, Monocyte chemoattractant protein 1; *MIP-1α*, macrophage inflammatory protein 1α.

expression was significantly increased in the airways of asthmatic subjects compared with that seen in healthy control subjects. A critical role for T_H17-related cytokines in airway remodeling has now been suggested, which could be due to interactions between these cytokines and structural cells.

Eosinophils play a critical role in tissue remodeling. They constitute the main source of the profibrotic cytokine TGF-β, which plays an important role in orchestrating tissue remodeling.[4,48] Moreover, eosinophils support fibroblast proliferation, collagen synthesis, and myofibroblast maturation.[49,50] In the airways of asthmatic subjects, IL-3, GM-CSF, and eotaxins 1, 2, and 3 drive the development of eosinophils from $CD34^+$ bone marrow precursor cells, whereas IL-5 enhances their maturation and recruitment into the airways.[51,52] Eosinophils are a rich source of granule basic proteins, ***eicosanoids***, ***cysteinyl leukotrienes***, tissue-damaging ***reactive oxygen species***, and a range of cytokines and chemokines.[53]

However, the central role of eosinophils in the inflammatory response of asthmatic patients has recently been challenged. Three injections of a humanized anti–IL-5 mAb given 2 weeks apart to asthmatic patients had a dramatic effect on circulating and sputum eosinophil counts but paradoxically did not affect any of the clinical outcome measures of asthma, including lung function.[54,55] Other studies, however, have demonstrated that eosinophil depletion through this approach was able to modify certain matrix proteins in the subepithelial basement membrane, such as tenascin C, lumican, and procollagen III.[56] Persistence of some eosinophils in asthmatic airway tissue despite IL-5 blockade could be due to the loss of IL-5 receptors on eosinophils on their recruitment into the airways.[57,58] These remnant eosinophils have been suggested to be responsible for sustained clinical manifestations of asthma. Other studies have clearly indicated that anti–IL-5 should only be administered to asthmatic patients with high eosinophil counts to be effective.[59]

Epithelial injury

Recent intensive investigations have changed our understanding of asthma from a purely inflammatory disease to a disease in which both inflammatory and functionally active structural components are equally involved. The bronchial epithelium represents the barrier that protects the internal milieu of the lung against external environmental factors.[28] Several reports have suggested that asthma primarily develops because of serious defects in the epithelial layer that allow environmental allergens, microorganisms, and toxins greater access to the airway tissue.[28,60] This injury to the epithelial layer in asthmatic patients is believed to be associated with an impaired repair process that drives the inflammatory and remodeling responses in the underlying submucosa.[61] Environmental (pathogens, allergens, pollutants, and cigarette smoke) or mechanical stress factors resulting in epithelial injury can also stimulate the release of mediators from the epithelium, which contributes to tissue remodeling. Holgate[20] and others have recently reported defective epithelial tight junctions in biopsy specimens from asthmatic patients and in association with impaired barrier function.

Several important mediators of remodeling, including TGF-β and chemokines, are released from damaged/repairing epithelium or in response to inflammatory mediators, such as IL-13. These mediators have been shown to play an important role in the development of subepithelial fibrosis and increased ASM mass.[48,62] This has led Holgate et al[63] to propose that asthma initially develops as a disorder in epithelial-mesenchymal interactions. Mesenchymal (structural), vascular, and neural networks play a critical role in airway development and are programmed to interact closely with the epithelium, defined as the epithelial-mesenchymal trophic unit. In fact, Holgate[60] has recently proposed that the epithelial-mesenchymal trophic unit becomes chronically reactivated in asthmatic patients, leading to a microenvironment that supports chronic inflammatory responses. An additional role of the epithelium in airway remodeling in patients with severe asthma has recently been shown by Johnson et al.[64] This study demonstrated that the epithelial-to-mesenchymal transition, which is classically considered to be primarily active during development, can occur in the airway epithelia of mice chronically exposed to an aeroallergen. In this process epithelial cells downregulate tight/adherens junction proteins; increase their expression of mesenchymal proteins, such as procollagen I and α-smooth muscle actin; and cross the basement membrane to take up residence in the airway submucosa. However, more research is needed to determine the physiologic contributions of the epithelium in the pathogenesis of asthma and to identify novel therapeutic targets able to protect the airways from asthma-triggering environmental factors.

Cell-cell interactions

Cell-cell interactions have been shown to be critical for the interaction of many inflammatory and structural cells leading to airway tissue remodeling. Mast cells have been reported to trigger the release of fibroblast-derived ***IL-6*** through direct cell contact.[65] In addition, Ramos-Barbon et al[66] have recently shown that $CD4^+$ T cells might directly enhance ASM proliferation through cell-cell interactions *in vivo*, resulting in increased airway hyperresponsiveness (AHR). Moreover, Lazaar et al[67] have shown that activated T lymphocytes can adhere to cultured ASM, an interaction that is mediated through ICAM-1, VCAM-1, and CD44 on ASM cells, leading to the upregulation of cell adhesion molecules and the stimulation of DNA synthesis in ASM cells.[68] Furthermore, other inflammatory cells, including eosinophils,[32] neutrophils,[69] and mast cells, were also shown to interact with ASM cells through ICAM-1 and VCAM-1.[31,70] These studies have clearly suggested that interactions of ASM cells with inflammatory cells through CAMs can directly contribute to tissue airway remodeling in asthmatic patients.

Inflammatory mediators

Inflammatory mediators, cytokines, chemokines, and growth factors released by inflammatory and structural cells are believed to be key players in initiating and synchronizing airway remodeling. Several mediators of remodeling have been identified thus far, including profibrotic cytokines (TGF-β and IL-11), T_H2 cytokines (IL-4, IL-9, IL-13, and IL-5), T_H17 cytokines (IL-17A, IL-17F, and IL-17E [IL-25]), epithelium-derived chemokines (RANTES, macrophage inflammatory protein 1α, IL-8, and eotaxin), and MMPs.[71]

TGF-β is a pleiotropic cytokine with different functions depending on the microenvironment or cellular conditions. Although many cell types secrete TGF-β, eosinophils constitute one of the main sources of this cytokine in asthmatic patients.[3,4,56] TGF-β has been shown to affect many structural cells *in vitro* and *in vivo* and has been implicated in the remodeling process in patients with asthma and other inflammatory and immune-mediated lung diseases.[64,72] TGF-β promotes the differentiation of fibroblasts to myofibroblasts[73] and induces the expression of MMPs and TIMPs, both of which are major regulators of ECM turnover.[74] Moreover, TGF-β has been shown to enhance the proliferation of ASM cells through the activation of the mitogen-activated protein kinase pathway.[75] Recently, we have reported a role for TGF-β in enhancing ASM cell migration toward the epithelium to form new bundles.[76] We have also shown that TGF-β, in the presence of platelet-derived growth factor, upregulates the expression of MMPs and TIMPs in ASM cells, thereby enhancing their migration.[76]

Other profibrotic cytokines, such as IL-11, have been shown to be involved in subepithelial fibrosis, airway wall thickening, myofibroblast differentiation, and smooth muscle cell proliferation. In fact, IL-11–transgenic mice have been shown to have asthma-like symptoms and hyperresponsiveness to methacholine.[77] We have also shown that the level of IL-11 expression correlates with asthma severity and subepithelial fibrosis, suggesting a role for this cytokine in enhancing airway remodeling.[78]

T_H2 cytokines, including IL-4, IL-5, IL-9, and IL-13, play critical roles in the development of airway remodeling in asthmatic patients. Allergen-specific T_H2 cells are thought to be present in the lung tissues of almost all patients with asthma, particularly patients with allergic asthma.[39] T_H2 cytokines regulate the allergen-specific synthesis of IgE (IL-4), the recruitment of eosinophils (IL-5), the recruitment and growth of mast cells (IL-9), and the regulation of AHR, a major feature of asthma (IL-13).[41] They also induce mucus gene expression in airway epithelial cells, trigger subepithelial fibrosis, and enhance hypertrophy of the epithelium.[62]

IL-17 is a newly discovered cytokine critical for the immune responses associated with severe asthma. The main IL-17 cytokines known to be involved in asthma are IL-17A, IL-17F, and IL-17E. The combination of TGF-β and IL-6 skews the balance toward differentiation of T_H cells into IL-17–producing T_H17 cells.[79,80] In addition to T_H17 cells, γδ T cells,[81] natural killer (NK) T cells,[82] neutrophils,[83] and macrophages[84] produce IL-17, which has been shown to be a potent neutrophil chemotactic agent.[85] IL-17E (IL-25) is expressed by lung epithelial cells after exposure to allergens,[86-88] as well as by activated eosinophils, bone marrow–derived mast cells, and basophils.[89] It has been detected in the eosinophil-infiltrated bronchial submucosa of asthmatic patients.[90] Several reports have indicated that IL-17E acts on both the innate and adaptive immune systems to amplify T_H2 immune responses.[91-93]

Chemokines have recently been shown to play a major role in the development of airway remodeling and can be expressed by a number of cell types in the lung, including epithelial cells[94,95] and ASM cells in asthmatic subjects.[96] In addition to their role in recruiting inflammatory cells to the site of inflammation, chemokines are able to mobilize airway structural cells and hence contribute to airway remodeling during asthma. ASM cells express receptors for epithelium-derived CC and CXC chemokines, such as CCR3, CCR1, CCR5, and CXCL1/2,[29,97,98] which, on stimulation by their ligands, induce the migration of ASM cells

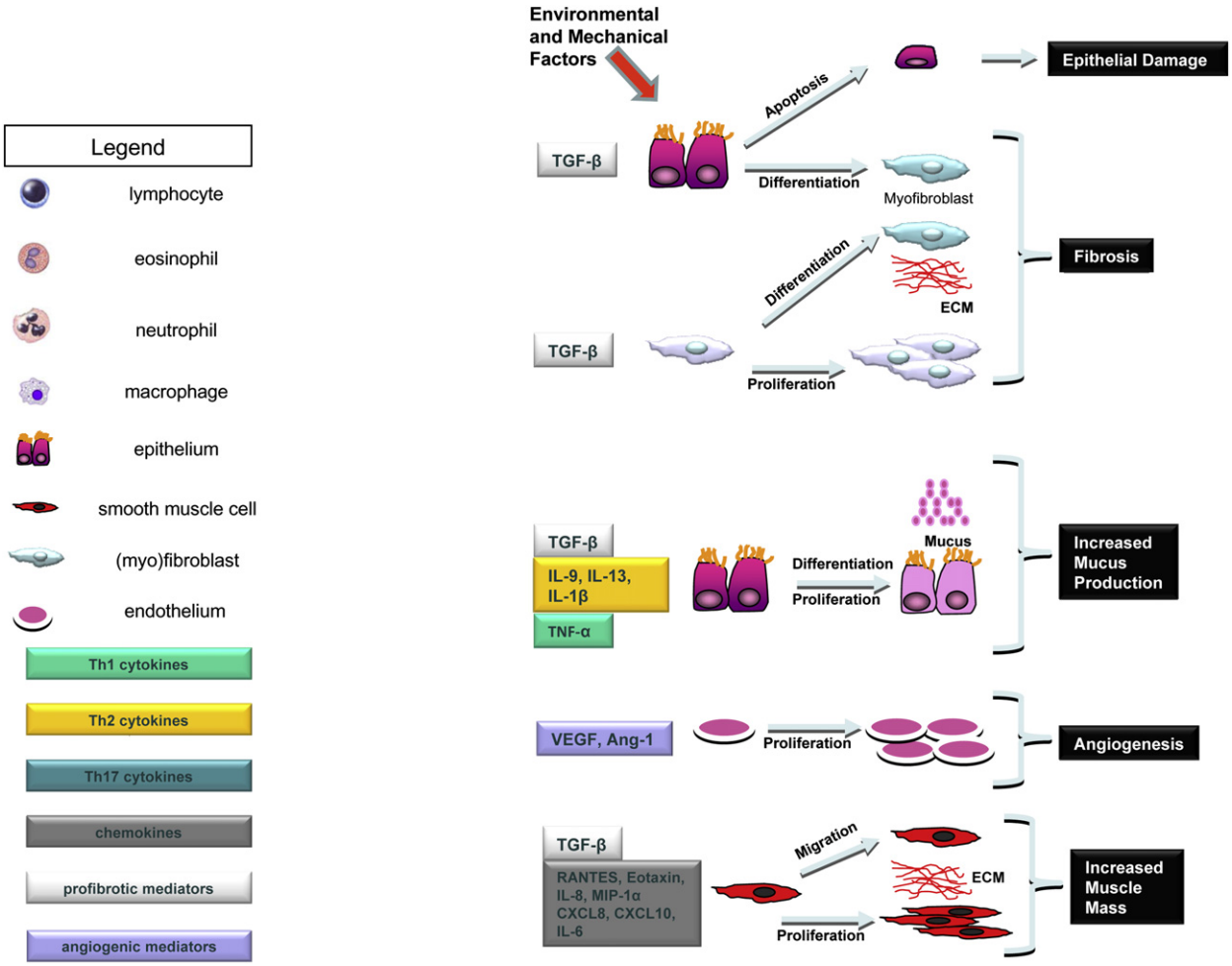

FIG 3. Mechanisms of airway remodeling in asthmatic patients. Asthma-associated inflammatory mediators exert their effects on different cell types in the lung, leading to fibrosis, excess mucus production, angiogenesis, and increased airway smooth muscle mass. *MIP-1α*, Macrophage inflammatory protein 1α.

toward the epithelium.[99] Furthermore, using a murine model of AHR, Gonzalo et al[100] have shown that neutralizing chemokines, such as eotaxin, RANTES, and monocyte chemoattractant proteins (MCPs), significantly reduced bronchial hyperresponsiveness, as well as leukocyte infiltration.

Imbalance between repair and removal of ECM proteins

ECM proteins form a network of collagenous and noncollagenous structures that surrounds cells in the airway tissue and affects many aspects of cellular behavior, including migration, differentiation, survival, and proliferation.[101] The main ECM elements include collagens, elastic fibers, fibronectin, and members of the MMP family (MMP-1, MMP-2, MMP-9, and MMP-12) in addition to TIMP-1 and TIMP-2, which are inhibitors of MMPs. Abnormal deposition of ECM elements has been described in the submucosal and ***adventitial*** areas of the large and small airways of asthmatic patients.[102-105] Although deposition of collagen IV and ***elastin*** is decreased in the airway walls of asthmatic patients, collagens I, III, and V; fibronectin; tenascin; hyaluronan; versican; and laminin α_2/β_2 chain levels are increased compared with those seen in healthy subjects.[23,106-109]

In addition to the submucosal and adventitial areas of the large and small airways,[102-105] ECM elements have been described within the ASM layer in fatal cases of asthma.[110] ASM cells secrete MMPs, as well as their regulators, TIMPs,[111] and hence contribute to the regulation of ECM composition. In fact, ECM composition within the ASM layer might constrain shortening of the ASM bundles and prevent excessive airway narrowing. Digestion of ECM proteins associated with ASM bundles results in increased force generation and shortening of ASM strips *ex vivo*.[112] Therefore fibrosis of the airway wall might protect against the collapse of the airway lumen by an exaggerated contraction of the increased ASM mass.

CLINICAL RELEVANCE OF REMODELING IN ASTHMATIC PATIENTS

Structural-physiologic relationship

Remodeling is assumed to result in persistent airflow limitation, a decrease in lung function, and AHR. Structural changes in the asthmatic airway (Fig 3), particularly increased smooth muscle mass, angiogenesis, and subepithelial fibrosis, have been correlated with airflow limitation.[113-115] Moreover, cellular infiltration in the asthmatic airways is associated with a decrease

in lung function.[116] The relationship between airway remodeling and AHR, on the other hand, is more elusive. A study on asthmatic children has demonstrated that the degree of bronchial hyperresponsiveness and presumably airway remodeling early in life is predictive of impaired lung function later.[117] However, although structural changes are thought to enhance AHR, especially increased smooth muscle mass in the asthmatic airway,[118-120] one study in patients with severe asthma has demonstrated that airway reactivity to methacholine is inversely correlated with airway wall thickening, as assessed by means of noninvasive high-resolution computerized tomographic scanning.[121] The mechanical properties of altered ASM are a plausible explanation for these surprising data.[122] Recently, Siddiqui et al[123] studied the mechanism of AHR in asthmatic patients and demonstrated that mast cell localization in ASM bundles, but not structural remodeling of the airway wall, was associated with AHR in asthmatic patients.

Asthma exacerbation and remodeling

The role of asthma exacerbations in airway remodeling has attracted many recent studies. The increased levels of proinflammatory cytokines and remodeling genes, including tenascin, procollagen I, procollagen III, heat shock protein 47, and α-smooth muscle actin, have been shown in endobronchial biopsy specimens from patients with mild asthma after allergen inhalation. Interestingly, although these inflammatory markers resolved within 7 days of the exacerbation, the remodeling markers persisted.[124,125] Additionally, although no histopathologic evidence of remodeling was documented, Bai et al[126] have demonstrated a greater decrease in lung function associated with a higher frequency of asthma exacerbations in nonsmoking patients with moderate-to-severe asthma who were followed for at least 5 years. Although low-dose inhaled steroids might reduce acute exacerbations in patients with mild persistent asthma, it seems that this intervention has no effect in mitigating the decrease in lung function.[127]

Viral infection and remodeling

Viral infections are major triggers of acute asthma exacerbations. Human rhinoviruses, including new species, are the most common triggers in children and adults.[128-130] After viral infection, an inflammatory cascade is initiated with significant release of inflammatory mediators, including proinflammatory cytokines, chemokines, interferons, and growth factors.[131,132] It has been recently shown that cultured epithelial cells infected with rhinovirus express markers that play major roles in remodeling, including amphiregulin (an epidermal growth factor that alters the repair process), activin A (a member of TGF-β superfamily), and VEGF (a major proangiogenic activator in asthmatic airways).[131,133] The susceptibility to viral infections in asthmatic patients is not limited to epithelial cells. In fact, rhinovirus has been detected in subepithelial layers and cells, including fibroblasts in asthmatic airways, probably because of a disrupted and inflamed epithelium.[134,135] It was recently found that fibroblasts from asthmatic patients enhance the replication of rhinovirus and induce a subsequent vigorous proinflammatory response with IL-6 and IL-8 production.[136] Furthermore, such rhinovirus replication was augmented in TGF-β–treated fibroblasts from asthmatic patients.[137] The cytopathic effects of viral infection on epithelial cells predispose to an acute inflammatory response and could enhance airway remodeling.[138-141]

Tobacco smoking and remodeling

Tobacco smoking is relatively prevalent among asthmatic patients, reaching up to 20%.[142] Its contributions to asthma severity, airway inflammation, accelerated decrease in lung function, and impaired responses to corticosteroid therapy have been recently recognized.[143-147] Several inflammatory and structural changes have been demonstrated in nonasthmatic smokers, which include increased cellular inflammatory infiltration; increased expression of certain cytokines, such as IL-1β and IL-8; and increased deposition of tenascin and laminin under the basement membrane.[148,149] However, little is known about the effect of smoking on structural changes in asthmatic airways. It has been shown that tobacco smoking can alter the inflammatory profile in asthmatic airways, as shown by abundant neutrophilia in the induced sputum of smoking asthmatic patients.[150]

In addition, the large airways of smoking asthmatic patients show reduced numbers of $CD83^+$ mature ***dendritic cells*** and B cells, which might render these patients less responsive to corticosteroid therapy and more susceptible to infection.[151] Moreover, increased expression of arginase I and ornithine decarboxylase in the airways of smoking compared with nonsmoking asthmatic patients has also been reported.[152] In a small but interesting study analyzing bronchial biopsy specimens from steroid-naive young patients with mild asthma, the bronchial mucosa from smoking asthmatic patients showed squamous cell metaplasia and increased expression of neutrophil elastase, IFN-γ, and IL-8, which might contribute to an impaired response to therapy and poor clinical outcome.[153]

Natural history of airway remodeling

Several studies have demonstrated that asthmatic patients experience an accelerated decrease in lung function more than healthy subjects and that this is proportionally related to the duration and severity of their disease.[143,154,155] However, other studies have reported that asthmatic children have poor lung function, suggesting that remodeling could start early in the course of the disease.[156-158] Despite the clear evidence that inflammatory changes start very early, as demonstrated in wheezing infants,[159-163] the onset of airway remodeling in asthmatic patients is not yet well characterized. No significant structural changes were seen in bronchial biopsy specimens from young children with wheezing and reversible airway obstruction.[164,165] However, a thickened reticular basement membrane, epithelial injury, and eosinophilic inflammation were evident by the age of 3 years.[166] These structural changes were consistently reported in children with moderate-to-severe asthma.[159,160,167,168] Large longitudinal cohorts have demonstrated that persistent wheezers (children with recurrent wheezing in the first 3 years of life and still wheezing at the age of 6 years) had significantly poorer lung function compared with late-onset wheezers (children who had wheezing at the age of 6 years but no wheezing before the age of 3 years). In both groups the loss in lung function was evident at the age of 6 years, with no major deterioration after that age.[155,169,170] On the other hand, data from the Childhood Asthma Management Program showed an accelerated decrease in lung function between the ages of 5 and 18 years in children with mild-to-moderate asthma.[171] On the basis of these functional and structural studies, Martinez[172] has suggested the concept of a "developmental window of opportunity" in the first 3 years of life in which abnormal inflammatory

responses to viruses could predispose to airway remodeling in patients with persistent asthma.

Therapeutic interventions and remodeling

Airway remodeling has been the focus of a significant amount of research in the last decade; however, the crucial question remains to be answered as to whether therapeutic intervention has any influence on remodeling.

Because of their effect on inflammatory modulation in asthmatic airways, inhaled corticosteroids (ICSs) have a great potential to influence airway remodeling. However, the available data to date are rather contradictory and elusive.[6] Several studies have demonstrated an *in vitro* antiproliferative effect of corticosteroids on ASM from asthmatic patients.[173-175] In addition to their apoptotic effects on airway epithelial cells,[176] corticosteroids have been shown to decrease the proliferation and inflammatory mediator release of lung fibroblasts.[177,178] Some studies have reported that ICS may reduce basement membrane thickness in airway biopsies from asthmatic subjects and may therefore influence subepithelial fibrosis, a major feature of remodeling.[179] On the other hand, other studies have reported a modest or no effect on basement membrane thickness.[180-183] These conflicting data could be related to the dose and duration of ICS therapy. Moreover, functional studies have failed to prove a substantial effect of ICS on inhibiting the decrease in lung function in patients with chronic asthma.[184,185] However, studies in asthmatic patients[186] and murine models of asthma[187] have demonstrated an effect of corticosteroids or combined corticosteroid/long-acting bronchodilator treatment on airway remodeling only in the context of allergen avoidance. Collectively, there is little evidence that corticosteroids can reverse airway remodeling in asthmatic patients.

Montelukast (a cysteinyl leukotriene receptor antagonist) is another medication used in the treatment of asthma that might have the potential to alter remodeling in asthmatic airways based on its anti-inflammatory effect.[188] Lymphocyte and myofibroblast counts have been shown to be diminished after allergen challenge in asthmatic subjects at the completion of 8 weeks of montelukast therapy.[189] Further long-term studies are required to clinically validate the potential antiremodeling effect of antileukotriene therapy in asthmatic patients.

Omalizumab, a humanized anti-IgE antibody, is a newly introduced treatment for severe asthma with steroid-sparing effects.[190] It has been shown to decrease IgE levels, sputum and tissue eosinophilia,[190,191] and circulating T_H2 cytokine levels and to improve lung function in patients with moderate-to-severe asthma[192]; however, no data are available to support the efficacy of anti-IgE therapy on airway remodeling.

Bronchial thermoplasty is a novel therapeutic intervention that alters airway structure by means of physical destruction of the smooth muscle and thereby affects airway remodeling.[193,194] However, the sustained effect of this intervention remains to be determined, although promising results of persistent improvement have been demonstrated 1 year after treatment.[193]

Tools to measure airway remodeling

As to the methods by which airway remodeling is assessed, asthmatic patients fall into 2 broad categories: invasive and noninvasive. Invasive methods involve direct sampling of the airway structure by the collection of biopsy specimens, often with an endoscope inserted into the bronchus through the nose or mouth. The flexible bronchoscope has been used since the 1960s as a diagnostic tool for the assessment of altered airway structure. This device can contain a number of tools and is capable of collecting various specimens, such as tissue biopsy specimens (with forceps or a needle), bronchial brushings, and bronchoalveolar lavage and can also be used to assess airway remodeling by means of endobronchial ultrasonography.[195] Although this procedure is safe, with low morbidity (0.1% to 2.5%) and very low mortality (<0.5%),[196] variability in the quality of the samples and the invasive nature of the technique limit its use for long-term assessment of the natural history of airway remodeling in asthmatic patients.

Noninvasive methods for assessing structural changes to the airway in asthmatic patients constitute a novel approach to investigating this aspect of the disease. Noninvasive imaging techniques used for this purpose include computed tomography (CT), magnetic resonance imaging,[197] and ***optical coherence tomography***.[198] Of these methods, CT is the most well characterized. This method can be used for qualitative description of various changes to lung structure, in particular airway wall thickening, in asthmatic patients.[199] Several studies have also performed quantitative assessments of airway remodeling by using this method,[200-202] and attempts have been made to correlate CT findings of airway remodeling to measures of lung function.[121] Interestingly, a combination of CT imaging and hyperpolarized ^{3}He magnetic resonance imaging has recently been used to investigate the regionality of airway structural changes in the lungs of asthmatic patients and to correlate these changes with functional alterations in airflow.[197] However, further studies in asthmatic patients with varying degrees of disease severity must be performed to fully validate these methods.

FUTURE DIRECTIONS

The last 2 decades have witnessed significant advances in our understanding of the pathogenesis of asthma. We have moved beyond the belief that asthma is an intrinsic abnormality of the airway myocyte to the belief that inflammation is the cornerstone of the pathogenesis of asthma. We now have evidence clearly indicating that functional abnormalities in asthmatic patients are the result of tissue remodeling responses and structural alterations in the airway. This concept, however, requires further testing and evaluation. We need to know how each of these features of the remodeled airway contributes to the symptoms, abnormal physiology, and natural history of asthma. More investigations are also needed to determine the types of interventions capable of altering the various features of airway remodeling and the effect of these interventions on the clinical manifestations of the disease. Moreover, we are in need of better pathophysiologic noninvasive tools and specific biomarkers that will help us precisely determine different subpopulations of asthmatic patients. More importantly, studies should to be directed at investigating the genetic factors associated with different types and degrees of tissue remodeling and the functional translation of these genetic modifications. These and other studies will profoundly affect our understanding of the pathogenesis of asthma and will shape the types of strategies we use to control asthma.

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