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Airway remodeling contributes to the progressive loss of lung function in asthma: An overview

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Airway inflammation, airflow obstruction, and bronchial hyperresponsiveness are characteristic phenotypic features of asthma. Clinically, airflow obstruction in asthma often is not fully reversible, and many asthmatic subjects experience an accelerated and progressive loss of lung function over time. Histopathologic studies of the asthmatic airway have demonstrated stereotypic changes that might explain the loss of lung function that many patients with asthma experience. The notion of airway remodeling in asthma postulates that the alteration of the structure and function of key airway constituents, including airway smooth muscle, epithelium, blood vessels, and mucus glands, might explain, at least in part, the progressive loss of lung function that is observed clinically. Inflammation driven by $CD4^+$ lymphocytes and mediated by effector cells, particularly the eosinophil, appears to modulate the function of mesenchymal cells, including fibroblasts and myofibroblasts, changing the composition of the airway wall matrix. Changes in the airway epithelium might alter the function of the underlying smooth muscle and the composition of the matrix and could drive inflammation. Alterations in the structure and function of airway smooth muscle change the mechanical properties of the airway wall and might also affect the function of other airway constituents. A variety of experimental models have identified candidate mechanisms and mediators for these observed changes, which are thus potential therapeutic targets. However, clinical studies to date have been disappointing, and it remains to be seen whether targeted therapies will prevent the progressive loss of lung function seen in asthma. (J Allergy Clin Immunol 2005;116:477-86.)

Key words: *Asthma, airway, remodeling, inflammation*

Asthma is a disease characterized by episodic airflow obstruction that is at least partially reversible; lung inflammation, particularly in the airways; and bronchial (airways) hyperresponsiveness (AHR). Detailed histologic and physiologic analyses of asthmatic subjects have demonstrated that both the structure and function of the airways are altered in asthma. Conceptually, airway remodeling in asthma includes not only structural changes but also fundamental changes in the relationships between and among various airway constituents. Cell-cell interactions, the regulation of cells by extracellular matrix, and the modulation of the composition of matrix by cells have all been demonstrated to be altered.

The presence of AHR implies a fundamental change in the function of airway smooth muscle (ASM) that is partially due to changes in ASM structure and its relationships with the surrounding airway wall structures. In addition, longitudinal studies have shown that asthmatic subjects demonstrate greater losses of lung function over time than nonasthmatic subjects,[1-3] and a consensus of expert opinion now agrees that irreversible airflow obstruction (in some ways similar to chronic obstructive pulmonary disease) might occur in asthma, a concept proposed many years ago as part of the so-called Dutch hypothesis.[4] Therefore the concept of airway remodeling in asthma can entail the histologic and structural changes associated with asthma, their physiologic consequences, and the progressive loss of lung function and permanent, irreversible airway obstruction that is observed in some patients with asthma. In this review we will focus on changes observed in ASM, inflammatory cellular

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Abbreviations used
AHR: Airways hyperresponsiveness
ASM: Airway smooth muscle
β_2-AR: β_2-Adrenergic receptor
MUC: Mucin glycoprotein
RBM: Reticular basement membrane
STAT: Signal transducer and activator of transcription
VEGF: Vascular endothelial growth factor

elements, bronchial epithelium, and subepithelium and describe their importance for the physiologic changes observed in asthmatic subjects.

MODELS OF AIRWAY REMODELING

A number of models have been used to characterize airway remodeling in asthma. Examination of lung tissues available at autopsy have shown that profound changes in airway morphology and structure have occurred in those that have died from asthma when compared with decedents with asthma dying from other causes and those without asthma.[1] *In vivo*, characterization of airway biopsy specimens from living subjects with asthma have been compared with those from control subjects. Many studies demonstrate stereotypical histopathologic changes associated with asthma, reversibility of some changes with corticosteroids,[5] changes in noninflammatory airway wall structures, and alterations in inflammatory cell distribution.[6,7] These studies are limited by the fact that bronchoscopic biopsy specimens are small and mostly limited to more proximal airway wall. The use of bronchoscopy and lung challenge models in human subjects has shown persistent changes in bronchoalveolar lavage components,[8] whereas in animals it has been shown that persistent changes in airway histopathology might occur after chronic airway challenge.[9]

Transgenic and knockout mouse models have revolutionized our understanding of airway remodeling by demonstrating that loss or gain in function of a gene product can correlate with airway structural and inflammatory changes that closely resemble those seen in asthma. Experimental systems involving cultured airway cells, including primary smooth muscle cells, fibroblasts, and epithelial cells, have been developed, and various end points have been examined that are related to airway remodeling. Among the functions examined are the regulation of cellular proliferation and cytokine and matrix component release and some of the relevant signaling pathways regulating those events.

ASM REMODELING

Airflow obstruction and AHR are a result of the contraction of ASM and hence indicate alterations in smooth muscle function. Several studies of patients dying from severe asthma have reported an increase in the apparent muscle mass within the airway wall in subjects with severe asthma when compared with control subjects.[1,10,11] In histologic studies an increase in mass is assumed when there is an increase in the cross-sectional area occupied by ASM. Subjects with fatal asthma have been reported to exhibit greater degrees of luminal narrowing and ASM mass when compared with patients with asthma experiencing nonasthma-related death. A reduction in the lumen area could be due to differences in lung inflation at the time of death, a concern voiced by critics of these studies. However, typically there is also an increase in the percentage of the airway wall area occupied by ASM in subjects with severe asthma, which also suggests an increase in muscle mass in these subjects. A direct relationship between duration of asthma or severity of asthma and the amount of ASM mass also appears to be present. For example, Bai et al[1] reported that older patients with fatal asthma had more muscle in the airway wall than younger patients with fatal asthma. Assuming that ASM mass is increased in asthma, several possible mechanisms could explain this finding: an increase in cell number (hyperplasia) resulting from increased cell proliferation or a reduction in apoptosis, cellular hypertrophy, and/or differentiation of other cell types into ASM cells, with subsequent migration into the muscle bundle.

Most of the available evidence supports ASM hyperplasia as an important mechanism leading to increased ASM mass in the asthmatic airway. A partial list of potential airway mitogens and factors that can affect ASM mass is presented in Table I.[12-14] Growth factors that engage receptor tyrosine kinases, a variety of agents that engage heterotrimeric G protein–coupled receptors, and other agents have been shown to be capable of inducing ASM hyperplasia. The majority of such studies that have identified these agents have been performed with cell culture models, and such models have allowed for the characterization of the signaling pathways mediating mitogen-induced ASM proliferation. These substances might be produced by resident airway cells, secreted by infiltrating inflammatory cells, or secreted by ASM, which could then act in an autocrine manner.[12] Most of these substances have been identified in bronchoalveolar lavage fluid and airway biopsy specimens or have been produced by airway cells collected from subjects with asthma. Cell culture models have allowed for the *in vitro* analysis of signaling pathways that regulate ASM proliferation.[13] Mitogenesis mediated by cytokines, receptor tyrosine kinase ligands, and G protein–coupled receptor ligands occurs through the phosphoinositide 3′-kinase[15] or the extracellular signal–regulated kinase[16] pathways. Accumulating evidence suggests that combinations of ligands can induce ASM proliferation *in vitro* in a synergistic manner.[17]

β_2-Adrenergic receptor (β_2-AR) agonists appear to attenuate ASM proliferation elicited by a variety of mitogenic stimuli. Additionally, ligands activating other G protein–coupled receptors coupled to Gs/adenylyl cyclase and hence promoting cyclic AMP generation appear to also attenuate mitogen-stimulated ASM proliferation.[18,19] Glucocorticoids have broad activity against a variety of