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# Pulmonary remodeling in asthma

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## Abstract

The inflammatory and immunologic processes responsible for asthma can produce permanently fixed obstructive lung disease unresponsive to medical therapy. This can be manifested clinically by the failure of a childhood asthmatic to reach full expected lung capacity at adulthood and by an accelerated decline in pulmonary capacity in adults. Recent studies have furthered our insight into the pathologic processes underlying these changes and the potential effects of therapy to prevent them.

## Introduction and context

Twenty years ago, asthma was universally thought of as a reversible, obstructive pulmonary disease. It was not until the 1990s that the concept that asthma could produce irreversible obstructive changes was introduced [1]. A search of the medical literature revealed only two references to pulmonary remodeling in asthma between 1990 and 2000. Today, a similar search reveals 1477 references. The structural changes that produce this irreversibility are damage to the epithelium, smooth muscle hyperplasia and hypertrophy, the deposition of glycoproteins in the parenchyma, the destruction of elastin, neovascularization, a thickened sub-basement membrane, and mucous gland hyperplasia [2].

It has now become clear that a significant number of asthmatics are at risk for development of these permanent changes, and that the degree of impairment produced by the remodeling process is clinically significant [3-5]. As many as 25% of childhood asthmatics are at risk for impaired lung growth [4] and as many as 16% of adult asthmatics exhibit a permanent and accelerated decline in lung function [5]. These changes can amount to a reduction of a liter or more in forced expiratory volume in one second ($FEV_1$) [6,7].

The underlying forces that drive the remodeling process consist of a panoply of inflammatory mediators that have destructive, restorative, and chemotactic properties and include, amongst many others, transforming growth factor beta, the metalloproteinases, eotaxin and other eosinophilic chemotactic agents, tryptase, histamine, elastase, and various interleukins (including IL-4, IL-5, IL-6, IL-9, and IL-13) [8-13]. The histologic changes characteristic of remodeling include smooth muscle hyperplasia, deposition of collagen and glycoproteins beneath the sub-basement membrane, goblet cell hyperplasia, airway epithelial cell proliferation and destruction, deposition of glycoproteins in the pulmonary parenchyma, and neovascularization.

Over the past several years, a number of risk factors have been identified that make it more likely that, in any given individual asthmatic, the remodeling process will occur [14,15]. These risk factors are listed in Table 1.

Finally, it should be made very clear that the process of remodeling in asthma is distinct from the pathogenesis that results in a similar decline in lung function in chronic obstructive pulmonary disease/emphysema [16]. Although the rates of decline in $FEV_1$ are similar in patients with fixed airflow obstruction caused by asthma to those with fixed airflow obstruction produced by emphysema, there are distinct differences between the two patient populations. Asthmatic subjects with fixed airway obstruction exhibit more exacerbations, higher

**Table 1. Factors associated with remodeling in asthma**

| |
|---|
| • Bronchial reactivity |
| • Duration of disease |
| • Severity of disease |
| • Presence of atopy |
| • Elevated levels of immunoglobulin E |
| • Eosinophilia |
| • Frequency of severe exacerbations |
| • Increased bronchodilator reversibility (a reflection of airway hyperreactivity) |

exhaled nitric oxide levels, and higher sputum eosinophil counts. In contrast, sputum neutrophil counts, comorbidities, and a diminished diffusion capacity are more characteristic of patients with emphysema [16].

Obviously, the goal of investigations into the remodeling process in asthma is to gain insights that would hopefully allow us to prevent or reverse these changes. Over the past few years, our knowledge in this regard has increased considerably.

## Recent advances

Advances have been made in our understanding of the ability of presently available treatments to favorably affect the remodeling process, allowing normal lung growth in children and preventing the accelerated decline in lung function in adults. Comparing clinical studies and other investigations into the mechanism(s) of the remodeling process, it has become evident that there may be distinct differences between the pathogenic mechanisms involved in the remodeling process in children versus those in adults and, therefore, distinct differences in their response to treatment.

Several recent clinical studies in children have been somewhat disappointing in terms of our present day ability to prevent the remodeling process and thus restore the normal rate of lung growth [17-19]. Taken as a whole, these three studies leave the distinct impression that inhaled corticosteroid therapy, although improving clinical parameters such as symptoms, pulmonary functions, and quality of life, do not seem to alter the potential for the diminished lung growth that occurs in childhood asthma. These studies are in contradistinction to older studies [20,21], as well as a more recent investigation [15], which demonstrated that the accelerated decline in lung function seen in many adult asthmatics can be diminished by regular administration of inhaled corticosteroids. In addition, this can be accompanied by improvement in the histopathology associated with the remodeling process in adults with this condition [20].

Perhaps the distinction between the failure to demonstrate enhanced lung growth in childhood asthma and the ability to diminish the accelerated decline in lung function in adult asthma could be related to differences in the pathogenesis of these two processes. It has been traditionally thought that the same remodeling process that produces an accelerated decline in lung function in adults also accounts for the diminished lung growth seen in childhood asthmatics. However, a recent investigation [22] casts doubt on this assumption. It has long been known that one of the characteristic features of the remodeling process in adults is the increased deposition of ground substances including fibronectin in the pulmonary parenchyma. It is thought that damage to the epithelium stimulates fibroblast activation below the basement membrane, and this results in the manufacture and deposition of a number of glycoproteins, including collagen.

In contrast, studies of bronchial epithelial damage in childhood asthma revealed that children with asthma, compared to healthy atopic control subjects and healthy nonatopic control subjects, demonstrate a reduced capacity of epithelial cells to manufacture fibronectin. Under normal circumstances, fibronectin assists in the repair process of bronchial epithelium. The authors found that childhood asthmatics had a diminished capacity to produce fibronectin as a result of an innate abnormality in bronchial epithelial cells. This contrasts sharply with the overproduction of fibronectin, as evidenced by deposits of this substance below the basement membrane, seen in the parenchyma of remodeled asthmatic airways. Fibronectin can be made by several different cell types that reside in the airways. These include fibroblasts, macrophages, and endothelial and epithelial cells. The precise source of the subbasement membrane fibronectin seen in adult asthmatics is unknown, but presumably the majority is produced by fibroblasts. Of course, this difference between adults and children regarding the deposition of fibronectin may not explain differences noted between these two groups in their response to inhaled coticosteroids (see below), but it is at least suggestive of this possibility.

## Implications for clinical practice

The findings noted above imply that in adults with asthma, early treatment with inhaled corticosteroids, administered on a daily basis and in sufficient doses, may have an impact on the remodeling process and therefore the accelerated decline in pulmonary function that occurs in a significant proportion of adult asthmatics.

Unfortunately, available studies to date have not shown that the use of inhaled corticosteroids favorably affects

the failure of childhood asthmatics to reach full lung growth. These observations and *in vitro* studies on epithelial repair imply that there may be separate pathogenic mechanisms involved in the remodeling process in adults and children. Nevertheless, at least at this point in time in adults, corticosteroids seem to be the most potent weapon we have against pulmonary remodeling in asthma.

## Abbreviations

$FEV_1$, forced expiratory volume in one second; IL, interleukin.

## Competing interests

The author declares that he has no competing interests.

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