Inhaled Corticosteroid Treatment and Extracellular Matrix in the Airways in Asthma

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Key Words
Asthma
Airways
Epithelium
Inflammation
Inhaled corticosteroid
Treatment
Extracellular matrix

Abstract
Even mild asthmatics with a short duration of the disease show at the morphological level a picture of chronic inflammation with airway epithelial changes and influx of inflammatory cells into the airway mucosa. Several studies have shown that inhaled corticosteroid treatment can ameliorate this inflammation. In addition, even a morphologically normal epithelial structure may be restored. However, factors which may lead to more chronic disease have remained obscure. Recent studies are now focusing on the reversibility of collagen deposition in the airway epithelial basement membrane. Airway epithelial and stromal interactions may be important when a change at this level occurs.

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Introduction
The discovery of the inflammatory nature of bronchial asthma even at an early stage of the disease has led to an increase in the clinical use of anti-inflammatory drugs in the treatment of asthma [1-6]. In addition to an increase in the number of inflammatory cells, structural epithelial changes have been described in asthma [2, 5,7]. The epithelium may have an important function in regulating the inflammatory process, and the interaction between the epithelium and the subepithelial basement membrane in the airways may play a crucial role in the pathogenesis of asthma.

cules are the glycoproteins of the integrin family of receptors. Various types of integrin receptors with different α and β subunits have been found in human airway epithelial cells [9]. So far, no changes at this cellular receptor site have been reported in asthma.

It was recently shown that a prominent feature in the airway mucosa of newly diagnosed asthmatics [7] is the change in the structure from a predominantly ciliated epithelium to goblet cell hyperplasia. Goblet cell hyperplasia may reflect a reaction to irritation or a cell maturation defect [10].

Extracellular Matrix in the Basement Membrane

Structural Epithelial Changes
A prominent feature in asthma is the marked airway oedema with shedding of airway columnar epithelial cells [8]. This shedding may be caused by a weak cellular attachment of adjacent columnar epithelial cells to each other or to the basal cells. Cell adhesion molecules help epithelial cells to maintain contact with their underlying stroma and with each other [9]. The best characterized of the cell adhesion molecule.

The basement membrane under the epithelium is a thin layer of specialized extracellular matrix not only providing mechanical support but also influencing cellular behaviour [11]. Interactions between the bronchial epithelium and the extracellular matrix proteins have been shown to play a significant role during the development of the structural organization of the lung [12]. During this process, the receptor site of the cells mediates signals from the matrix inside the cell which in turn may alter cell secretion. Several glyco-

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proteins such as fibronectin and tenascin are involved in this process. They are considered to be transitional components of the basement membrane, because in adult lung their expression is sparse or negative. However, in asthma, tenascin is re-expressed in the airway basement membrane [13], possibly reflecting increased turnover of the airway epithelium. Several investigators have described a thickened basement membrane to be characteristic of asthma [4, 8, 14]. Because the thickening of epithelial basement membrane in asthma is partly due to increased expression of various collagens, this could be one mechanism leading to persistence of the disease.

Effects of Inhaled Glucocorticosteroid Therapy on Airway Morphology

Several studies have examined the effects of inhaled corticosteroids on the airway morphology, using bronchial biopsy techniques. Laursen et al. [15] have reported the effects of 11 months treatment of severe asthmatics with inhaled budesonide (1,600 µg/day). The treatment was not associated with connective tissue atrophy. Jeffery et al. [16] showed in an uncontrolled study, that 4 weeks treatment of atopic asthmatics with budesonide reduced airway inflammation, but even prolonged treatment (up to 3.7 years) could not reduce the thickening of the reticular basement membrane. Laitinen et al. [6] demonstrated in a controlled study, that 3 months therapy with inhaled budesonide (1,600 µg/ day) reduced the overall inflammation, and this decrease in the inflammatory reaction was associated with restoration of the normal epithelium.

In our recent study [13], where the effect of inhaled budesonide on subepithelial fibrosis in birch-pollen-sensitive seasonal asthmatics was evaluated by immunohistochemis-try using monoclonal antibodies against collagen types III, IV and VII, we could not find any change in the thickness of the collagen band. However, the glycoprotein tenascin content in the basement membrane area decreased significantly in the steroid-inhaling group in comparison to the placebo group. This suggests that the inflammation but not the fi-brotic process in the basement membrane is prevented by inhaled steroids. However, controversial results have been published. In a very recent study, Trigg et al. [17] reported that 4-months inhalation treatment with beclometasone di-propionate reduced both airway inflammation and subepithelial collagen III deposition in mildly asthmatic patients.

Acknowledgement
This work was supported by the Paulo Foundation, Finland, and The Finnish Anti-Tuberculosis Association Foundation.

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Laitinen/Laitinen
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