

The airway epithelium in childhood asthma

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Key words: *Bronchial epithelium, nasal epithelium, remodeling*

There has been a focus for more than 40 years on the bronchial epithelium as an important structure in initiating the physiologic and clinical abnormalities of asthma.¹ This makes sense because the bronchial epithelium is the initial barrier met by all inhaled irritants, toxins, or allergens, and the bronchial epithelium's response to these noxious stimuli might be important for the subsequent elimination of these stimuli. An initial series of experiments suggested that the loss of the "tight barrier" function of the epithelium with the consequent exposure of irritant nerves,¹ enhanced access to intraepithelial mast cells,² or both was the most important epithelial abnormality in asthmatic patients. It was also obvious from bronchial biopsy specimens in adult asthmatic patients that the bronchial epithelium was structurally abnormal, with a marked increased number of goblet cells in the epithelium in asthmatic patients³ and a suggestion that the epithelium was more friable and easily detached from the basement membrane.⁴ Moreover, the bronchial epithelial damage was correlated to the degree of airway hyperresponsiveness in asthmatic patients.⁴

Subsequently, it has become clear that the bronchial epithelial cell is not merely a passive player in initiating bronchial responses to allergens or irritants. An example of this is the fact that epithelial cells have the ability to transition into mesenchymal cells,⁵ which can contribute to airway remodeling, a characteristic of asthma. This response involves the production of growth factors belonging to the fibroblast growth factor, epidermal growth factor, and TGF- β families and the phenotypic transformation of epithelial cells into fibroblasts, which have the ability to produce extracellular matrix proteins involved in airway remodeling. The characteristic changes of airway remodeling include not only changes to the epithelial cell structure but also deposition of extracellular matrix proteins below the basement membrane, increases in airway blood vessels, and an increase in airway smooth muscle. These changes of airway remodeling occur very early in

the development of the disease in children⁶ or even in patients with allergic rhinitis before asthma manifests clinically.⁷

The functional consequences of airway remodeling are airway hyperresponsiveness, irreversible airflow obstruction, or both. Evidence collected from longitudinal follow-up of patients with childhood asthma indicates that a major component of the irreversible component of airflow obstruction in asthmatic patients develops early in disease progression⁸; however, in most patients the irreversible airflow obstruction does not relentlessly progress as asthmatic children grow into adult life.⁸ Taken together, these observations would suggest that most of the important changes in airway structure and function develop very early in the development of asthma.

A study published in the current issue of the *Journal*⁹ has shed some light on how the bronchial epithelium in asthmatic children might initiate structural and functional changes. Both bronchial and nasal epithelial cells from children with mild asthma, atopic nonasthmatic patients, and healthy control children were studied. These authors describe that both bronchial and nasal epithelial cells from the asthmatic children showed an increase in periostin expression and produced more TGF- β 2 and vascular endothelial growth factor compared with levels seen in the other 2 groups. Furthermore, levels of TGF- β 2 and periostin, but not vascular endothelial growth factor, were further increased when stimulated with IL-4 and IL-13. All these proteins have previously been implicated in airway remodeling. TGF- β 2 is important for fibroblast differentiation and activation, and vascular endothelial growth factor is important for new vessel formation, whereas periostin can activate TGF- β signaling and stimulate fibroblasts. Of interest, expression of a disintegrin and metalloproteinase 33, levels of which have been demonstrated to be upregulated in patients with moderately severe asthma,¹⁰ was not different between the groups. The study is the first to demonstrate that the bronchial epithelium from children with mild asthma produces factors that might promote airway remodeling and airway hyperresponsiveness.

Studies have found that inhaled corticosteroids (ICSs) improve bronchial epithelial cell morphology in asthmatic patients¹¹ and that treatment early in the disease can prevent the irreversible change in lung function.¹²⁻¹⁴ In addition, some components of airway remodeling, such as increased reticular basement membrane thickness, can be modified by ICSs.¹⁵ However, there are no studies that demonstrate that early treatment with ICSs attenuates the epithelial production of proremodeling factors and that this is associated with alteration of the airway structure and its functional consequences. In the study by Lopez-Guisa et al,⁹ the markers of airway remodeling were similar in patients treated with ICSs and those who did not receive ICSs; however, the study does not allow any conclusions about the role of ICSs in inhibiting the production of these markers or influencing airway remodeling. This is because the epithelial cells were several passages removed from ICSs before the measurements were obtained and because the *in vivo* airway structure was not evaluated.

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Disclosure of potential conflict of interest: P. M. O'Byrne has received speaker's honoraria from AstraZeneca; is on advisory boards for AstraZeneca, GlaxoSmithKline, Boehringer, Merck, and Almiral; and receives research support from AstraZeneca, Asmacure, Genentech, Amgen, ONO, and AIM. S. Pedersen receives lecture fees from GlaxoSmithKline and is on advisory boards for GlaxoSmithKline, Boehringer Ingelheim, and Nycomed.

Received for publication February 20, 2012; accepted for publication February 21, 2012.

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J Allergy Clin Immunol 2012;129:998-9.
0091-6749/\$36.00

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doi:10.1016/j.jaci.2012.02.030

The asthmatic children studied were described as having mild asthma, presumably of a rather short duration. However, as a group, they had slightly but significantly reduced FEV₁ values and a significant reduction in FEV₁/forced vital capacity ratios when compared with the other 2 groups. Some, but not all, of the asthmatic children demonstrated bronchodilator reversibility; therefore the findings of enhanced proremodeling epithelium-derived factors in patients with childhood asthma are consistent with previous observations that both airway remodeling and its functional consequences occur very early in the course of asthma.⁶

Another important observation made by Lopez-Guisa et al⁹ was that there was a reasonably good correlation between the cytokine production measured from the bronchial and nasal epithelial cells. Obtaining bronchial epithelium for research purposes is very challenging in both adults and children because it involves fiberoptic bronchoscopy. The knowledge that both bronchial and nasal epithelial cells are functionally similar with regard to their propensity to produce proremodeling factors will help future research on mechanisms for the increased production of these cytokines and their pharmacologic manipulation.

Irreversible airflow obstruction occurs early in the course of asthma,⁸ but in many (but not all) patients it does not progress to severe airflow obstruction as asthmatic patients age. The reasons for this lack of progression in airflow obstruction in some, but not all, patients are entirely unexplained and deserving of more study. One possibility would be to compare the airway epithelium's ability to produce proremodeling factors in patients with new-onset childhood asthma compared with those in adult asthmatic patients with either reduced or well-maintained lung function. With the new information about the correlation between cytokine production from nasal and bronchial epithelial cells, this question might also be elucidated in long-term studies assessing the clinical effect of asthma and different treatment modalities on the decrease in lung function, the course of airway hyperresponsiveness, or changes in asthma control in well-characterized groups of patients by studying nasal rather than bronchial epithelial cells.

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