

Unraveling the Mysteries of the Asthmatic Airway Epithelium

Asthma encompasses a set of disease states of varying etiologies and phenotypes. Clinical and functional phenotypes are clearly associated with changes in the inflammatory state and/or in the airway structure (1). Structural changes occur in the airways of patients with asthma of different degrees of severity and contribute to fluctuations in airway hyperreactivity and/or to the development and progression of persistent airway obstruction (2). The major components that drive the process of airway remodeling include increases in airway smooth muscle, angiogenesis, extracellular matrix and collagen deposition, and epithelial damage. Undoubtedly, the epithelium represents a major site of airway remodeling, and damage to the epithelium by allergens, viruses, or pollutants can stimulate the release of factors that regulate airway inflammation and stromal cell deposition of extracellular matrix proteins (3).

Activin A is a member of the transforming growth factor- β superfamily, which contributes to both inflammation and remodeling. Although there are conflicting data regarding the role of activin A in the regulation of asthmatic airway inflammation, its role in airway remodeling is clear (4). Activin A induces lung fibroblast proliferation and differentiation into myofibroblasts, and stimulates the production of collagen (5, 6). Follistatin is a protein that binds activin with high affinity and low reversibility (7). Follistatin antagonizes the pleiotropic actions of activin by diminishing damage associated with inflammation and fibrosis. This was first shown in an animal model in which intranasally administered follistatin—before allergen exposure—inhibited the production of T-helper cell type 2 cytokines and the induction of subepithelial collagen and smooth muscle deposition through inhibition of activin A (8). In another study, remodeling changes were prevented in a house dust mite model of asthma by injection of a neutralizing anti-activin A antibody before challenge (9). In this issue of the *Journal*, James and colleagues (pp. 104–113) present some new mechanistic data relevant to the asthmatic epithelium (10). The authors report that follistatin-like 3 (FSTL3), a glycoprotein secreted by bronchial epithelial cells that binds to and inhibits activin A, is diminished in media from epithelial cells cultured from children with asthma compared with those cultured from healthy subjects. This suppression of FSTL3 release was further amplified when airway obstruction was present. The authors go on to propose a mechanism by which decreases in FSTL3 expression by the asthmatic bronchial epithelium lead to subepithelial fibrosis through an activin A-mediated stimulation of fibroblast proliferation and fibroblast-to-myofibroblast transition. Interestingly, they found no significant differences in activin A levels released by cultured epithelial cells from children with asthma versus healthy children. To determine whether eosinophilic inflammation is associated with the alterations in activin A or FSTL3 secretion, they measured the fractional exhaled nitric oxide (FE_{NO}), which is typically increased in association with airway inflammation. Although the FE_{NO} levels were higher in subjects with asthma, there was no correlation between the FSTL3 levels secreted by the cultured cells and the FE_{NO} levels measured in the

subjects. To further explore the underlying mechanisms, they experimentally suppressed FSTL3 expression in bronchial epithelial cells, and observed an increase in collagen deposition and fibroblast-to-myofibroblast transition. In related studies, they found that knockdown of activin A led to decreased fibroblast-to-myofibroblast transition.

Despite its strengths, some limitations to the study are worth noting. First, FE_{NO} is not a definitive measure of eosinophilic inflammation (11). Accordingly, the lack of correlation between FE_{NO} and activin A or FSTL3 does not exclude a role for eosinophils. Their results contrast with the findings of a clinical study in which sputum activin A levels showed a positive association with eosinophils, as well as features of airway remodeling such as reticular basement membrane thickening and levels of TGF- β 1, in patients with severe asthma (12). In the same study, no significant associations were detected between sputum or BAL fluid levels of follistatin and measures of inflammation or airway remodeling.

Second, the study population was not homogeneous, as the children with asthma may not have been optimally or identically treated. Moreover, apart from the presence of mild or no airflow obstruction, no information regarding control status and exacerbation history is provided. Importantly, the influence of allergen exposure and viral infection was not examined in terms of their effect on the activin A–FSTL3 imbalance. Indeed, human rhinovirus infection of airway epithelial cells leads to upregulation of activin A, thus linking the infection with early induction of remodeling and possibly increased asthma risk (13).

Despite these concerns, a major strength of this study is that it provides evidence regarding the mechanism of airway remodeling in terms of an imbalance between activin A and FSTL3 signaling, whereby diminished FSTL3 expression leads to subepithelial fibrosis.

Two questions arise. First, is a simple imbalance between two antagonizing factors sufficient to drive airway remodeling? Second, can we build treatment strategies based on this imbalance? It is possible that the different FSTL3 levels observed between patients with asthma and normal lung function and those with airway obstruction are due to the fact that airflow limitation is in part a consequence of airway remodeling, whereas preserved lung function may just represent the result of a repair process. This issue is difficult to address because the number of children with asthma and differences in lung function was relatively small. Finally, the higher levels of FSTL3 expression could reflect an antiinflammatory response to counterbalance the amplified inflammation, as activin A can stimulate FSTL3 expression by acting in an inhibitory feedback loop to reduce its activity (14, 15).

Based on the recently published American Thoracic Society statement on airway remodeling (3), we still have to consider the mechanisms that drive airway remodeling at the different sites of the airways. We must also define whether these mechanisms simply enhance progression, whether they represent therapeutic targets, and, finally, whether they differ according to the

disease severity and also within the various phenotypes and endotypes. The study by James and colleagues provides a start to answering these questions and also raises issues for further clarification. ■

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