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AN IN VIVO MODEL OF HUMAN AIRWAYS FOR INVESTIGATING FIBROSIS

S Ferrante,¹ T Hackett,² C Hoptay,¹ J Engelhardt,³ J Ingram,⁴ Y Zhang,³ S Alcala,¹ F Shaheen,² E Matz,¹ D Pillai,¹ R Freishtat¹. ¹*Children's National Medical Center, Washington, DC, United States;* ²*Centre for Heart Lung Innovation, St Paul's Hospital, Vancouver, BC, Canada;* ³*University of Iowa, Iowa City, IA, United States;* ⁴*Duke University, Durham, NC, United States*

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Purpose of Study Limited models exist to investigate the airway epithelium's role in repair, regeneration, and pathology of chronic obstructive lung diseases. We introduce a human asthmatic airway epithelial xenograft system integrating a proliferating and differentiating airway epithelium with an actively remodeling rodent mesenchyme in an immunocompromised murine host. We hypothesized that epithelial regeneration in asthma induces underlying matrix fibrosis.

Methods Used Human airway epithelial cells from asthmatic and non-asthmatic donors (n=5 per group) were seeded into decellularized rat tracheas. Tracheas were ligated to a sterile tubing cassette and implanted subcutaneously in the flanks of athymic nude mice. Grafts were harvested at 2, 4, or 6 weeks for analysis of tissue histology, fibrillar collagen deposition, and TGFβ1 activation. Non-transplantable human lungs from asthmatic and non-asthmatic donor FFPE sections were analyzed using similar methods.

Summary of Results Grafted epithelial cells generated a differentiated epithelium with basal, ciliated, and mucus cells. By 4 weeks post-engraftment, asthmatic-derived epithelia showed decreased numbers of ciliated cells and E-cadherin expression compared to non-asthmatic controls, similar to human lung biopsy tissue. While there was no evidence of matrix remodeling in acellular xenografts, grafts seeded with asthmatic-derived epithelial cells had 3 times as much fibrillar collagen at 6 weeks post-engraftment as non-asthmatic epithelial seeded grafts. This was accompanied by a >2-fold induction of matrix TGFβ1 [with evidence of pSMAD3 activity] in asthmatic grafts at 4

weeks (positive pixels/total field pixels= 0.12 ± 0.001 vs. 0.05 ± 0.001 ; $p=0.003$) and 6 weeks (0.09 ± 0.02 vs. 0.04 ± 0.01 ; $p=0.044$) post-engraftment.

Conclusions We show in this model that asthmatic epithelium alone is sufficient to drive aberrant mesenchymal remodeling, specifically with fibrillar collagen deposition in asthmatic-derived xenografts. These xenografts are a major advance over current animal models of asthma in that they permit direct assessment of the epithelial-mesenchymal trophic unit.