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MITOTIC ASYNCHRONY INDUCES A PRO-INFLAMMATORY STATE IN AIRWAY EPITHELIUM

S Alcalá,¹ A Benton,¹ A Watson,¹ E Reeves,² J Damsker,² Z Wang,¹ K Nagaraju,¹ M Rose,¹ E Hoffman,² R Freishtat¹. ¹Children's National Medical Center, Washington, DC, United States; ²ReveraGen Biopharma, Rockville, MD, United States

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Purpose of Study Mitotic behaviors are likely important for maintaining and restoring homeostasis in lung diseases with epithelial injury. We recently proposed that regenerative asynchrony in repairing tissue may underlie chronic inflammation and fibrosis, where immune cell infiltration is secondary to pro-inflammatory cross-talk among asynchronously repairing adjacent tissues. Building on our previous finding that regenerative asynchrony is associated with pro-inflammatory/fibrotic cytokine secretion, here we provide proof of cause-and-effect.

Methods Used *In vitro* experiments were performed wherein airway epithelial cells were mitotically asynchronous due to disease state and then resynchronized via capture of the G₁/S checkpoint via pulse exposure to dexamethasone, simvastatin, or aphidicolin. Experiments utilized a novel method we developed for inducing mitotic asynchrony in normal progenitors. Induced populations were used to elucidate if TGF- β 1 plays a role in the resynchronization process.

Summary of Results Human asthmatic fully-differentiated air-liquid interface airway epithelial mitosis was asynchronous relative to normal epithelia. Mitotic capture increased the percentage of progenitors in G₁. This resynchronization in the asthmatic epithelia reduced basolateral TGF- β 1 secretion. We next examined whether inducing mitotic asynchrony in normal epithelial cells would result in TGF- β 1 secretion. Mitotic asynchrony was induced and samples showed moderate asynchrony at 6 and 12 hours that resolved spontaneously by 48 hours. These cells show elevated TGF- β 1 secretion at 12 hours compared to either cell population in isolation. Regulation of TGF- β 1 is being investigated as a possible mechanism for synchronization through contact and non-contact dependent experiments. Additionally, blocking TGF- β 1 delays resynchronization.

Conclusions Cumulative analysis shows mitotic synchrony is the homeostatic state in airway epithelial progenitor populations and poorly-synchronized mitosis (as in asthma) induces TGF- β 1 secretion and a pro-inflammatory/pro-fibrotic airway. This finding establishes rationale for targeting progenitor cell mitotic behavior rather than immune-mediated inflammation in fibrotic disease.