The role of Interleukin-1 in driving inflammation and remodeling in the asthmatic-EMTU

Introduction
Asthma is a chronic inflammatory disease of the airways that is associated with airway remodeling, which involves all tissues of the airway wall including the epithelium, sub-mucosal, smooth muscle layers and vascular structures. In particular, a well documented feature of airway remodeling in asthma, is the accumulation of fibroblasts/ myofibroblasts in the epithelial-mesenchymal trophic unit (EMTU) that leads to the deposition of excess collagen in the lamina propria of the airways. Our previous work has shown that airway epithelial cells, through the production of IL-Iα, regulate the fibroblasts within the lung EMTU.

Specific Aim
The aim of this study was to assess the effects of epithelialderived IL-Iα on fibroblastinduced inflammation, ECM production and remodeling within the asthmatic EMTU.

Methods & Materials
Primary airway epithelial cells (PACs) and primary airway fibroblasts (PAFs) were obtained from both asthmatic and non-asthmatic donors using tracheal biopsies harvested through the International Institute for the Advancement of Medicine. PACs were cultured at airliquid interface (ALI) for 20 days. RNA & supematant were harvested at days 0, 5, 11, 20 of ALI culture & the expression and release of IL-Iα and other β-1 family members was determined by RNA sequencing and ELISA respectively. PAFs were seeded on collagen I gels stimulated with 1mg/ml IL-1α, IL-1β, IL-33 or media control for 24 hrs as described below in figure 1. PAFs were also seeded on collagen I coated plates and stimulated with 1ng/ml IL-1α, IL-1β, IL-33 or media control for 24 hrs. RNA was harvested for qRT-PCR and the release of pro-inflammatory mediators was measured using ELISA.

Collagen I gel contraction assay

IL-1 stimulates inflammatory & growth factor release from airway fibroblasts

IL-1 induces decreased ECM and Gli-1 expression in airway fibroblasts

IL-1 controls fibroblast repair phenotype by regulating Lysyl oxidase (LOX) & microtubule formation

CONCLUSIONS
Airway Epithelium in Asthma

There is an increased production of IL-1α in the repairing asthmatic airway epithelium.

IL-1α and IL-1β but not IL-33 induce inflammatory cytokine release and downregulate ECM production through Gli-1 in airway fibroblasts.

IL-1 inhibits lysyl oxidase expression leading to inhibition of collagen I contraction potentially through inhibition of the fibroblast microtubule cytoskeleton.

This may contribute to increased inflammation as well as defective remodeling of the Collagen I in the asthmatic EMTU.

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