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Title: Do characteristic airway epithelial change precede the development of lung fibrosis? Ectopic epithelial marker protein expression in bleomycin induced fibrosis replicates that seen in bronchiolized epithelium in IPF

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Body: The cause Idiopathic Pulmonary Fibrosis (IPF) remains elusive but there is support for the view that epithelial cell damage within the peripheral lung initiates the process that ultimately results in fibrosis. Unfortunately, markers of this process remain elusive due in part to most human studies being performed with tissues from end-stage disease. Ectopic expression of the gel forming mucin, MUC5B was recently described as a specific marker for the bronchiolized epithelium seen in IPF and we have shown that it is co-expressed in this region with LPLUNC1 but not with other airway submucosal gland proteins, including Zinc-alpha2-glycoprotein and Proline-rich protein 4. To shed light on a temporal association of expression of these markers with fibrosis development we studied mice exposed to the pro-fibrotic agent bleomycin (Bleo). MUC5B and LPLUNC1 were co-expressed in a population of goblet cells in the airways of mice within 3-7 days of Bleo exposure, prior to the onset of a fibrosis. Continued expression is seen during the development of fibrosis between 14-21 days post treatment. In contrast, in mice treated with PBS neither protein was seen (due to mouse airways being essentially free of goblet cells). Staining was absent from the fibrotic regions and the lung parenchyma, as is the case in IPF. Our data show that the ectopic expression seen in human IPF is mirrored by that seen in the Bleo mouse model. Furthermore it suggests that these epithelial remodeling events precede the development of lung fibrosis and these can be studied in mice.