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Absence of Periplakin protects from lung fibrosis after bleomycin injury in mice

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RATIONALE: Chronic injury of the alveolar epithelium and subsequent activation of aberrant repair is central to the pathophysiology of idiopathic pulmonary fibrosis (IPF). Alteration of desmosomal junctions may be responsible for loss of lung epithelium integrity and fibrogenesis. A previous study of our group identified periplakin, a cytolinker between intermediate filament scaffolding and the desmosomal plaque as a specific target of autoimmunity in IPF.

OBJECTIVES: To determine the role of PPL during lung injury and remodeling.

METHODS: Effects of PPL deficiency in $Ppl^{+/+}$ and $Ppl^{-/-}$ mice was explored using the mouse model of lung fibrosis induced by intratracheal instillation of bleomycin. Survival, lung injury, repair and fibrogenesis were assessed by analyzing body weight, lung histology, morphometric analysis and BALF composition (cellularity and cytokines) and collagen content. Regulation of periplakin and its cellular partners were determined in vitro in MLE15 cells and primary mouse type II cells (AEC) in response to proinflammatory (TNFalpha, IL1beta) and profibrotic (TGFbeta, PDGFbb) mediators, and to bronchoalveolar lavage fluid (BALF) from patients with IPF.

MEASUREMENTS AND MAIN RESULTS: We observed that periplakin levels were significantly reduced (54%±3, $p<0.02$) in $Ppl^{+/+}$ mice following bleomycin induced injury. Using MLE15 cells and primary AEC, we showed that both *Ppl* mRNA levels and protein expression were decreased (40%±3, $p<0.008$) within 24 hours in the presence of BALF from IPF. This decrease was also observed in response to either TGFbeta, PDGF-BB, IL1beta or TNFalpha. We identified binding sites for two transcription factors Klf5 and Egr2 that regulate PPL expression in the lung. While Klf5 increased PPL expression in a dose-dependent manner, Egr2 had an opposite effect. $Ppl^{-/-}$ mice were protected from lung injury. PPL deficient mice had improved survival 14 days after bleomycin instillation (70% vs. 50% in $Ppl^{-/-}$ mice, $p<0.0001$). Lung fibrosis was reduced in $Ppl^{-/-}$ mice with a decreased in collagen deposition ($p<0.004$) and ECM protein expression. While total BAL cell count was similar in groups, neutrophil and lymphocyte recruitment was decreased in $Ppl^{-/-}$ mice. Integrity of the epithelial barrier was better preserved in $Ppl^{-/-}$ mice as early as day 3 till day 14 after bleomycin injury. Expression of profibrotic mediators, including CTGF (30%±3, $p<0.001$) was decreased in both BAL cells and lung tissues from $Ppl^{-/-}$ mice.

CONCLUSION: Suppression of PPL expression reduced lung fibrosis after bleomycin injury, suggesting that PPL may play a role in the alveolar epithelium by mechanisms others than desmosome formation.