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Title: Altered proliferation of alveolar epithelial cells is involved in progressive elastase-induced emphysema

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Body: RATIONALE: Chronic obstructive pulmonary disease (COPD) is characterized amongst others by development of emphysema. We showed that a single application of porcine pancreatic elastase (PPE) causes a severe progressing emphysema-like phenotype in C57BL/6 mice. Since the development of emphysema is apparently not completed after PPE application, we aimed to identify possible key mechanisms that drive this process even at late time points. METHODS: Female C57BL/6 mice received a single oropharyngeal application of PPE or PBS, and lung function, histology and gene expression were analyzed on days 2, 28, 56, and 162. Fibroblasts of PPE treated mice were characterized analyzing mitochondrial membrane potential. Furthermore, LA-4 lung epithelial cells were treated with PPE and proliferative and apoptotic characteristics were measured using gene expression or wound healing assays. RESULTS: PPE treated C57BL/6 mice develop progressive airway enlargement and impairment of pulmonary function during 23 weeks of analysis. Q-PCR revealed elevated expression of apoptosis markers, reduced proliferation and increased expression of matrix components. Lung fibroblasts of PPE treated mice show reduced proliferation and an altered mitochondrial membrane potential. Reduced proliferation was also found in PPE treated LA-4 cells. CONCLUSION: Diminished proliferation in PPE treated lung epithelial cell lines as well as in lungs and primary fibroblasts of PPE treated mice could explain the persistent progression of PPE induced emphysema in mice.