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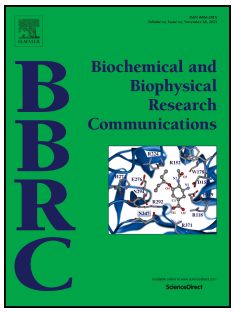

Muc1 deficiency exacerbates pulmonary fibrosis in a mouse model of silicosis

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Muc1 deficiency exacerbates pulmonary fibrosis in a mouse model of silicosis

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ABSTRACT

Background: MUC1 (MUC in human and Muc in animals) is a membrane-tethered mucin expressed on the apical surface of lung epithelial cells. However, in the lungs of patients with interstitial lung disease, MUC1 is aberrantly expressed in hyperplastic alveolar type II epithelial (ATII) cells and alveolar macrophages (AM), and elevated levels of extracellular MUC1 are found in bronchoalveolar lavage (BAL) fluid and the serum of these patients. While pro-fibrotic effects of extracellular MUC1 have recently been described in cultured fibroblasts, the contribution of MUC1 to the pathobiology of pulmonary fibrosis is unknown. In this study, we hypothesized that MUC1 deficiency would reduce susceptibility to pulmonary fibrosis in a mouse model of silicosis.
Methods: We employed human MUC1 transgenic mice, Muc1 deficient mice and wild-type mice on C57BL/6 background in these studies. Some mice received a one-time dose of crystalline silica instilled into their oropharynx in order to induce pulmonary fibrosis and assess the effects of Muc1 deficiency on fibrotic and inflammatory responses in the lung.
Results: As previously described in other mouse models of pulmonary fibrosis, we found that extracellular MUC1 levels were markedly increased in whole lung tissues, BALF and serum of human MUC1 transgenic mice after silica. We also detected an increase in total MUC1 levels in the lungs of these mice, indicating that production as well as release contributed to elevated levels after lung injury. Immunohistochemical staining revealed that increased MUC1 expression was mostly confined to ATII cells and AMs in areas of fibrotic remodeling, illustrating a pattern similar to the expression of MUC1 in human fibrotic lung tissues. However, contrary to our hypothesis, we found that Muc1 deficiency resulted in a worsening of fibrotic remodeling in the mouse lung as judged by an increase in number of silicotic nodules, an increase in lung collagen deposition and an increase in the severity of pulmonary inflammation.
Conclusions: Altogether, our results indicate that Muc1 has anti-fibrotic properties in the mouse lung and suggest that elevated levels of MUC1 in patients with interstitial lung disease may serve a protective role, which aims to limit the severity of tissue remodeling in the lung.

Keywords
KL-6, Muc1 mucin, silicosis, lung injury, pulmonary fibrosis, inflammasome