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Title: Immunoproteasome expression in pulmonary fibrosis

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Body: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease with unknown cause ultimately leading to death. It is believed that repetitive microinjuries of the alveolar epithelial cells initiate chronic wound healing and immune responses which ultimately leads to pulmonary fibrosis. Immunomodulatory cytokines such as IFNγ and IL17 contribute to disease pathogenesis. Only recently, the IFNγ inducible immunosubunits of the proteasome have been shown to affect regulation of adaptive immune responses. Here, we investigated the expression pattern and possible involvement of immunoproteasomes (IP) in pulmonary fibrosis. To study regulation of IP in lung cells in vitro, we analyzed expression of IP subunits LMP2 and LMP7 in different cell lines and primary mouse and human lung fibroblasts. IFNγ induced pronounced expression of IP in all examined cell types. Expression levels of LMP2 and LMP7 were evaluated in wildtype (wt) as well as $LMP2^{-/-}$ and $LMP7^{-/-}$ mice in whole lung homogenate. Of note, we observed pronounced expression of IP subunits in wt lungs compared to other organs. Expression of IP was induced in bleomycin-induced pulmonary fibrosis and remained elevated even during tissue repair. Notably, immunohistochemical analysis of lung sections of human donor (n=6) or IPF patients (n=7) revealed expression of LMP2 in alveolar macrophages and interstitial cells in both donor and IPF. LMP2 positive alveolar epithelial cells, however, were only detected in IPF lungs. We are currently investigating the causal role of LMP2 in pulmonary fibrosis using LMP2 deficient mice. Elevated levels of IPs in pulmonary fibrosis might add to disease course by affecting adaptive immune responses in the lung.