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Title: Proteasome function in lung fibrosis

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Body: The proteasome is a multicatalytic protease complex responsible for the degradation of proteins in numerous cellular processes. Inhibition of the proteasome has been shown to provide antifibrotic effects in different organs. The mechanisms of these antifibrotic actions are not well understood but suggest a role of proteasome function in the pathogenesis of fibrosis. We hypothesize, that proteasome activity is abnormally regulated and involved in mediating profibrotic effects in lung fibrosis. To analyze a profibrotic role of the proteasome, CCL206 fibroblasts were treated with TGF-β1 and proteasome activities were examined using specific luminescent substrates and native gel. Proteasome activities were significantly increased in TGF-β1 treated cells without changes in expression of proteasome subunits on mRNA or protein levels. This increase in activity could be blocked by specific proteasome inhibitors and was associated with reduced fibroblast proliferation and collagen deposition. These findings were confirmed in primary lung fibroblasts. Only the regulatory subunit Rpn6, proposed to serve as a key regulator in the assembly of highly active 26S proteasomes, was elevated on protein level. Proteasome activities and Rpn6 levels were also significantly increased in fibrotic lungs of bleomycin-treated mice. We are currently performing siRNA knockdown of Rpn6 to analyze its causal role for mediating TGF-β1 induced proteasome activation. Increased proteasome activities in TGF-β1 treated fibroblasts and in fibrotic mouse lungs propose a major role of the proteasome in profibrotic processes. This might be caused by Rpn6, mediating the formation of more active proteasome complexes and therefore contributing to the pathogenesis of lung fibrosis.