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Increased protein turnover contributes to the development of pulmonary fibrosis

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Scientists of the Comprehensive Pneumology Center (CPC) at the Helmholtz Zentrum München have identified a new mechanism which contributes to the development of idiopathic pulmonary fibrosis (IPF). They showed that the pathological changes of lung tissue are accompanied by an increase in protein turnover by the central protein degradation machinery of the cell – the proteasome. Their study has now been published in the *American Journal of Respiratory and Critical Care Medicine*.

Idiopathic pulmonary fibrosis is a very aggressive form of pulmonary fibrosis and has a particularly poor prognosis. This fatal disease, for which so far no causal therapies exist, is characterized by a massive deposition of connective and scar tissue in the lung, which leads to a progressive loss of lung function and ultimately death. Connective tissue is mainly produced by myofibroblasts. The research group led by PD Dr. Silke Meiners of the Institute of Lung Biology and the CPC showed now for the first time that the activation of these myofibroblasts depends on increased protein turnover by the 26S proteasome.

Inhibition of the proteasome as a possible therapeutic approach

In the recently published study, the Helmholtz scientists were able to demonstrate an activation of the 26S proteasome during the transformation of normal fibroblasts into myofibroblasts both in vitro

and in vivo using two different experimental models of pulmonary fibrosis. Moreover, increased protein turnover was also detected in fibrotic lung tissue of IPF patients. "Conversely, we were able to show that targeted inhibition of the 26S proteasome prevents the differentiation of primary human lung fibroblasts into myofibroblasts, confirming the essential role of enhanced proteasomal protein degradation for this pathological process," said Silke Meiners.

"Understanding the mechanisms that lead to a disease such as IPF helps us identify innovative approaches that allow therapeutic intervention," comments Professor Oliver Eickelberg, director of the Institute of Lung Biology and scientific director of the CPC. In further studies, the Helmholtz scientists want to test the therapeutic use of substances which specifically inhibit the 26S proteasome, but do not affect other proteasome complexes in the cell. Furthermore, the lung researchers speculate that activation of the 26S proteasome may generally occur in fibrotic diseases, such as heart and kidney fibrosis, since differentiation of fibroblasts into myofibroblasts also is the underlying mechanism for the pathological alterations in these disorders.

The 26S proteasome is a kind of molecular shredder that breaks down old or defective proteins of the cell into their recyclable components. It consists of a catalytic core, the 20S proteasome, and one or two 19S regulators that bind to both ends of the 20S complex and mediate specific degradation of ubiquitin-tagged proteins. It is assumed that a majority of the proteins in the cell are degraded in this way.

As shown in the study, by use of siRNA, which targeted a specific, essential subunit of the 19S regulator, the targeted inhibition of the 26S proteasome successfully suppressed a differentiation of fibroblasts into pathological myofibroblasts. This approach is significantly more specific than the use of catalytic proteasome inhibitors, which inhibit all active proteasomes, that is 26S and 20S proteasome complexes, in an entirely

non-targeted way. Apart from their use to treat malignant tumor diseases, proteasome inhibitors are controversial because of their toxic side effects. The specific inhibition of the 26S proteasome here represents a novel and far more specific approach through which unwanted side effects could be reduced, since preferably cells are attacked that show an activation of the system. In further studies, the scientists want to test the therapeutic use of substances that interfere specifically with 26S proteasome activity. These are molecules that prevent the assembly of the high-molecular-weight 26S proteasome from the 20S complex and the 19S regulators. Furthermore, a compound screening is planned for new substances that induce a specific 26S proteasome inhibition.

More information: "Regulation of 26S proteasome activity in pulmonary fibrosis," *American Journal of Respiratory and Critical Care Medicine*, DOI: 10.1164/rccm.201412-2270OC

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