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Title: Regulation of immunoproteasomes by cigarette smoke

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Body: Cigarette smoke (CS), as a major source for oxidative stress in the lungs, is the main cause of chronic obstructive pulmonary disease (COPD). Patients suffering from COPD are more susceptible to viral infections resulting in acute exacerbations. Viral infections induce expression of immunoproteasomes (IP) via IFNγ-signaling. This specialized form of proteasome is destined to improve antigen presentation in infected cells and to efficiently degrade oxidatively damaged proteins. The role of IPs in COPD pathology is unknown. Expression levels of IP-subunits LMP2 and LMP7 were evaluated in wildtype (wt) as well as $LMP2^{-/-}$ and $LMP7^{-/-}$ deficient mice in whole lung homogenates. Of note, we observed pronounced expression of IP-subunits in wt lungs compared to other organs. Immunohistochemical analysis of lung sections revealed that IP positive staining was observed in cells adjacent to airways, but also in alveolar regions. To study regulation of IP in vitro, we analyzed expression of IP in different lung cell lines. IFNγ induced pronounced expression of IP in both lung epithelial and fibroblasts cells, as detected by qRT-PCR and western blotting. We then investigated regulation of IP by CS. A549 human lung epithelial cells were treated with extracts of CS for 24h up to 12 days, and expression of IP was investigated on RNA and protein level. Long-term treatment of cells with CS-extract resulted in downregulation of basal IP expression. In vivo, wt mice exposed to CS for 3 days also showed significant downregulation of IP on the protein level. Diminished expression of IP due to smoke exposure may affect antigen processing of viral proteins and thus add on severity and delayed resolution of viral infections in COPD exacerbations.