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Title: A short-term model of COPD identifies a role for mast cell tryptase

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Body: Chronic obstructive pulmonary disease (COPD) represents a group of diseases that are difficult to treat effectively, with cigarette smoke (CS) being the main causative agent. COPD is currently irreversible, and often continues to develop even after smoking cessation. Lack of suitable models that represent the key features of the disease in a reasonable amount of time have been lacking, which would aid in the development of appropriate therapies. We have developed a mouse model of CS-induced COPD that manifests key components of the human disease. These mice develop inflammation, mucus hypersecretion, airway remodeling as well as emphysema, accompanied by reduced lung function after 8 weeks of exposure. These characteristic features of COPD were glucocorticoid-resistant and did not spontaneously resolve. In addition, smoke induced systemic effects including changes in skeletal muscle and the heart, and increased susceptibility to respiratory infections also were observed. As tryptases can play an important role in tissue destruction and lung homeostasis, we determined whether mast cell (MC)-derived protease-6 affected disease, and whether it effected activation of key immune cells. We demonstrate here that key disease aspects are significantly reduced in MC-derived protease-6 deficient mice. In addition, macrophages are also required for disease development. MC-derived protease-6 mediated its effects partly through the induction of pro-inflammatory cytokines from macrophages, including TNFα, CXCL1 and IL-1b. This model can be used to further our knowledge of mechanisms involved in and effect of therapies on COPD development.