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COPD 2016: Pharmacological and genetic approaches determine protease and oxidative stress as exacerbating factors in a mouse model of obstructive lung diseases_Tsuyoshi Shuto_Kumamoto University, Japan

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Protease-antiprotease imbalance and oxidative stress are considered to be the main pathophysiological features of severe lung disease, including chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), but their role in regulating obstructive mucus phenotypes , including pulmonary emphysema and dysfunction of βENaC - transgenic mice (Tg), a mouse model of COPD / CF, are unknown. Here, analysis of the DNA chips revealed that the protease-dependent and oxidative stress pathways are activated in the lung tissue of βENaC-Tg mice. Treatments of βENaC-Tg mice with a serine protease inhibitor ONO3403 and an antioxidant N-acetylcysteine significantly improved pulmonary emphysema and dysfunction. In addition, the depletion of a murine endogenous antioxidant in vitamin C (VC), by genetic disturbance of the synthesis enzyme of the senescence marker protein-30 (SMP30) in βENaC-Tg mice, increased the inflammatory status. in lung tissue and exaggerated pulmonary emphysema with a significant decrease in lung function, possibly due to an increase in oxidative stress. Our results define protease and oxidative stress as factors that exacerbate the obstructive mucus phenotypes of a mouse model of COPD / CF.

Pulmonary emphysema and dysfunction are pathophysiological features of severe obstructive pulmonary disease, including chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). In these disorders, defective clearance of mucus, excessive inflammation, protease-antiprotease imbalance and oxidative stress have been considered to influence severity. Given that COPD is one of the leading causes of morbidity and mortality worldwide and that cystic fibrosis is the most common lethal inherited disorder in Caucasians, the identification of key molecules and pathways underlying the pathogenesis of the disease has been the subject of extensive research for many years. Experimentally, the ideal mouse model that exhibits critical COPD / CF pulmonary phenotypes, such as mucus obstruction, goblet cell metaplasia, neutrophilic inflammation, and poor bacterial clearance, has been uniquely established by inducing a specific overexpression in the respiratory tract of the β subunit of the epithelial Na + channel in mice (βENaC-Tg mice). Above all, the same group further revealed by histological and morphological analysis that the βENaC-Tg mice not only exhibit an emphysematous phenotype but also a pulmonary dysfunction, and these pulmonary anomalies were strongly associated with those generally observed in patients suffering from COPD and cystic fibrosis. ENaC is a sodium ion channel that is expressed in the apical membrane of polarized epithelial cells, especially in the lung, kidney (mainly in the collecting tubules) and the colon. An over-activation of ENaC by a targeted overexpression of βENaC on the respiratory tract leads to the generation of a concentration gradient of sodium ions (for example, sodium ions going from outside to inside the cell) followed overabsorption of water in the cells, which leads to deregulation of mucus production and clearance of the respiratory tract.Based on evidence showing that expression and function of ENaC were inversely associated with lung function in patients with cystic fibrosis and could be increased in patients with COPD, βENaC-Tg mice could be tools valuable for exploring the obstructive phenotypes of COPD mucus and cystic fibrosis in vivo. However, the mortality of βENaC-Tg mice with a mixed C3H / HeN: C57 / BL6N background was extremely high5, which limits the use of the original βENaC-Tg line as an animal model of acute and fulminant respiratory diseases . It is important to note that Livraghi-Butrico et al. Have shown that the genetic background of βENaC-Tg mice strongly affects the survival and severity of the disease in mice. Because Johannesson et al. Also clearly demonstrated that C57 / BL6 backcrossing improved survival, βENaC-Tg mice with a C57 / BL6 background could be considered as an ideal animal model which represents the phenotypes of obstructive human respiratory diseases.

However, despite growing evidence of their usefulness in COPD and cystic fibrosis research, the importance of C57 / BL6-βENaC-Tg mice has only been demonstrated by a few groups around the world, suggesting that a comprehensive analysis to determine the specific molecules and pathways which could contribute to the pathogenesis of C57 / BL6-βENaC-Tg mice are also necessary.

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