European Respiratory Society
Annual Congress 2013

Abstract Number: 4792

Publication Number: P661

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: COPD - mechanism **Keyword 2:** Epithelial cell **Keyword 3:** Animal models

Title: Involvement of coactivator associated arginine methyltransferase 1 (CARM1) in development of elastase-induced progressive emphysema

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Body: Chronic obstructive pulmonary disease comprises chronic bronchitis and emphysema. Emphysema is characterized by destruction of alveolar walls leading to enlarged air spaces and reduced surface area. CARM1-an arginine methyltransferase and a coactivator to regulate transcription, translation and DNA repair is found important for regulating proliferation and differentiation of pulmonary epithelial cells (O'Brien, 2010). We wanted to investigate its role in emphysema development and progression. Porcine pancreatic elastase (PPE) was applied to C57BL/6 mice. Lung function, histology and gene expression were analyzed on day 2, 28, 56, and 161. CARM1+/- mice were analyzed on day 28. LA-4 alveolar cells were treated with CARM1 siRNA. Proliferative, apoptotic characteristics were measured by gene expression or wound healing assays. PPE-treated wild-type mice showed significant increased forced residual capacity, total lung capacity, dynamic lung compliance and decreased Tiffeneau index correlated to increased mean linear chord length (Lm) in a time dependent manner. qRT-PCR showed decreased proliferation (Cyclin D1) and increased apoptosis marker (Bax) in lung. CARM1 expression was significantly diminished. PPE-treated CARM1+/- mice displayed impaired lung function and enhanced Lm compared to wild type. Furthermore, silencing of CARM1 by siRNA in LA-4 cells led to reduced migration and proliferation. PPE treated wild type mice developed progressive emphysema and impaired lung function during 161 days of analysis. CARM1+/- mice showed to be more susceptible to emphysema progression. Pharmacological implication of CARM1 could be a prospectus therapy for COPD.