The Role of MFAP4 in the Pathogenesis of Pulmonary Emphysema

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**Objectives**

MFAP4 deficient mice spontaneously develop an emphysema-like pulmonary phenotype and we hypothesise that MFAP4 plays a protective role in the pathogenesis and progression of elastic defects and remodelling processes associated with development of pulmonary emphysema.

**Background**

Pulmonary emphysema is a progressive disease characterised by alveolar destruction and persistent inflammation of the airways which leads to airspace enlargement and tissue remodelling. Emphysema is thought to originate from imbalance between serine proteases, such as neutrophil elastase (NE) and their inhibitors. NE is known to degrade components of pulmonary extracellular matrix (ECM), including elastin and type I-IV collagens.

**Results**

- **Figure 1.** Localization of MFAP4 in human lung tissue. A) MFAP4 immuno-reactivity corresponds to the interalveolar septa of elastic fibrils. Black arrows indicate the presence of MFAP4 in elastic fibres (EF). Pictures adapted from Schlosser et al. 2006.
- **Figure 2.** Pulmonary function test and Micro-computed X-ray tomography (Micro-CT) of 8-month-old MFAP4 deficient mice (KO) and corresponding wildtype (WT) littermate mice support that the KO mice spontaneously develop an emphysema-like phenotype. The flexiVent (SCIREQ) system was used for analysis of the pulmonary function in tracheotomized mice. Results are expressed as mean ±SEM. Statistical significance was detected by t-tests: *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
- **Figure 3.** Pulmonary function tests on day 21 after administration of porcine pancreatic elastase (PPE) or PBS in MFAP4 deficient (KO) and corresponding wildtype (WT) littermate mice. The flexiVent (SCIREQ) were used for analysis of the pulmonary function in tracheotomized mice. Results are expressed as means ±SEM. Statistical significance was detected by two-way ANOVA followed by the Turkey’s test for comparisons between multiple groups: *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
- **Figure 4.** Total cell count in bronchoalveolar lavage (BAL) at day 21 after administration of porcine pancreatic elastase (PPE) or PBS in wildtype (WT) mice. Results are expressed as means ±SEM. Statistical significance was detected by two-way ANOVA followed by post-hoc analysis with the Turkey’s test for comparisons between multiple groups: *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
- **Figure 5.** Cellular composition in bronchoalveolar lavage (BAL) at day 21 after administration of porcine pancreatic elastase (PPE) or PBS in MFAP4 deficient (KO) and corresponding wildtype (WT) littermate mice. Results are expressed as means ±SEM. Statistical significance was detected by two-way ANOVA followed by post-hoc analysis with the Turkey’s test for comparisons between multiple groups: *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.

**Conclusion**

Compliance (Crss) and total lung capacity (A) were significantly increased in 8-month-old MFAP4 deficient mice compared to the wildtype mice. The inspiratory capacity (IC), compliance (Crss), and total lung capacity (A) were significantly increased in the untreated 8-10 week-old MFAP4 deficient compared to the wildtype mice. The PPE-treatment did not change the pulmonary function in the MFAP4 deficient mice to the same extend as in the wildtype mice. The data suggest that MFAP4 deficiency evokes spontaneous development of emphysema and we will now further investigate the integrity of the elastic fibrils.

**Methods**

Breath-hold gated Micro-CT Imaging:

8-month-old female C57BL/6N MFAP4 gene-deficient and corresponding wildtype littermate mice were subjected to breath-hold gated Micro-computed X-ray tomography (MicroCT) using the flexiVent (SCIREQ) system as ventilator.

Porcine pancreatic elastase (PPE) model:

8-10 week-old female C57BL/6N MFAP4 gene-deficient and corresponding wildtype littermate mice received 0.75 U PPE by oropharyngeal aspiration at day 0, 7 and 14. At day 21 the mice were sacrificed and different end-points were collected: lung function measurements (in living mice), bronchoalveolar lavage (BAL), serum from heart blood, and lung tissue for histology.