Rhinovirus application on the background of allergic airway inflammation in a chronic house dust mite model

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Rationale: Human rhinovirus (HRV) is most prominently associated with asthma exacerbations in humans. The U-BIOPRED project of the Innovative Medicine Initiative (IMI) aims to define biomarkers of asthma exacerbations for distinct phenotypes to enable a better prediction of therapeutic efficacy. In this context, mouse models of asthma with exacerbations induced by respiratory viruses are required for translational evaluation of biomarkers and therapeutic targets. The aim of this study was to establish an asthma exacerbation model by using HRV1b infection on the background of a chronic model of allergic airway inflammation against house dust mite (HDM).

Methods: BALB/c mice were sensitized intranasally with HDM extract (25µg in 50µl saline) for five days per week over 7 weeks. Control groups received saline. HRV1b was inoculated intranasally on the final three challenge days 30 minutes prior HDM application. 24h after the last combined virus/allergen challenge, pulmonary function (lung resistance, RL) was measured invasively to assess airway hyperresponsiveness (AHR) against aerosolized methacholine (MCh). Bronchoalveolar lavage (BAL), lung histology and restimulation of mediastinal lymph nodes were performed.

Results: A marked allergen-induced AHR (ED₁₀₀RL: 0.13 ± 0.05 vs. 0.34 ± 0.05 µg MCh for 100% increase in RL) and a strong allergic airway inflammation characterized by eosinophilic infiltration (3.80 ± 0.51 x10⁵/mL vs. 0.01 ± 0.003 x10⁵/mL) were induced in the HDM group compared to saline control group. Additional rhinovirus application with this protocol did not affect BAL differential cell counts. During lung function measurements, viscous mucus production was observed in the virus group and AHR was increased slightly but not significantly (ED₁₀₀RL: 0.09 ± 0.02 in HRV1b vs. 0.13 ± 0.05 in HDM+sham group). Mediastinal lymph node cell counts were increased in the virus group compared to non-infected allergic animals (6.12 ± 0.73 x10⁶/mL vs. 3.93 ± 0.4 x10⁶/mL).

Conclusions: The established model represented partly signs of exacerbating asthma pathology. While classical airway inflammation parameters were not affected, clinical signs of virus induced exacerbation were obvious by the health condition of the affected animals not clearly translated to valid read out parameters. As steroid insensitivity of asthma patients is an important problem in treatment of the disease, steroid efficacy will be investigated next in this model to establish a complete model for preclinical drug testing.

Funded by the Fraunhofer Society and the EU & EFPIA within the Innovative Medicines Initiative (IMI)