A mechanistic study of cigarette smoke-induced COPD in C57BL/6 mice: the impact of switching to pMRTP


*Philip Morris International, Philip Morris Products S.A., Neuchâtel, Switzerland; **Histovia GmbH, Schöne Aussicht 5, 5141 Overath, Germany

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder characterized by a progressive, not fully reversible airflow obstruction, which is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The main risk factor for this disease is tobacco smoking, whose pathogenic action may be potentiated by other harmful agents such as air pollution and individual susceptibility. Suitable animal models play an important role in the understanding of the smoke-induced pathogenesis of COPD. It has been shown that the C57BL/6 mouse strain is a useful tool for the mechanistic investigation of this disease (Chycz et al., 2008). Previously we have demonstrated that the chronic exposure of C57BL/6 mice to the aerosol generated by the reference cigarette 3R4F at a concentration of 750 µg/ml total particulate matter (TPM) resulted in emphysematous changes as early as after 2 months. Development of the progression of the pathology and the impact of cessation (switching from 3R4F aerosol to filtered air) have been followed at the molecular, cellular and tissue level for up to 7 months of exposure (manuscript in preparation). This study assessed the impact of switching from the exposure to cigarette smoke from 3R4F to the aerosol generated by the prototypic modified risk tobacco product (pMRTP) or filtered air. To assess the development of emphysema we evaluated pulmonary inflammation and function, histopathological changes, and a multi-platform of molecular changes (transcriptomics, proteomics, and lipidomics) at months 1, 2, 3, 4, 5 and 7.

Study design and end points

The mice were exposed to 3R4F (750 µg/ml TPM), pMRTP (matched to the nicotine in 3R4F – 34.4 µg/l) or filtered air for 4 hours per day, 5 days per week, for up to 7 months. After 2 months of exposure to 3R4F, switching and cessation groups were exposed to pMRTP or filtered air, respectively. Animals were observed on a daily basis, body weight progression was monitored twice per week, exposure parameters (including haemoglobin in blood and nicotine metabolites in urine) were measured 3 times during the study. Dissections were performed after 1, 2, 3, 4, 5 and 7 months of exposure. At each time point animals were allocated for the following end points: BALF (bronchoalveolar lavage fluid), for identification of infiltrated inflammatory cells in lungs and multi-analyte profiling; histopathological evaluation and morphometry of lungs, lung function and ‘omics’ (transcriptomics and lipidomics).

Conclusions

- The exposure to 3R4F cigarette smoke resulted in significant levels of pulmonary inflammation, decline in pulmonary function, and histopathological changes; these phenotypic changes were coherent with the molecular data.
- Chronic exposure to an aerosol from the pMRTP was found in every single change in all measured parameters when compared to the filtered air exposed animals.
- A biological response of switching to a pMRTP aerosol or filtered air following 2 months of 3R4F cigarette smoke exposure were very similar between the two conditions across the spectrum of endpoints assessed, and showed a generally positive effect.
- Differential gene expression associated with 3R4F exposure returned to a filtered air baseline level following either switching to a pMRTP aerosol or filtered air.
- Histopathological assessment also showed a marked effect of switching, in which a partial or complete (depending on the inflammatory cell type) reversal of pulmonary inflammation was observed.
- These data collectively indicate a halting or regression of the disease gene expression following switching.

References


PMI RESEARCH & DEVELOPMENT

Philip Morris International Research & Development, Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland