Respiratory irritants cause reversible up-regulation of pro-inflammatory cytokines on human nasal mucosa reconstituted in vitro

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Respiratory irritants are considered as substances of higher risk, at the same level as carcinogens, mutagens and toxic chemicals for reproduction. However, until now there is no validated in vitro cell model for identifying the respiratory chemical irritants. The aim of this study is to develop an in vitro cellular assay for identification of respiratory chemical irritants based on human 3D nasal airway epithelium (MucilAir™). Epithelia were reconstituted with primary human nasal cell pool from 14 donors. MucilAir™ is not only morphologically and functionally differentiated; but it can also remain at a homeostatic state for more than one year, allowing repeated dose and long term toxicity testing.

11 chemical compounds belonging to 3 classes (irritants "H335", Fatal if inhaled "H330", and non-toxic chemicals through inhalation) were tested. The cytotoxic effects of these chemicals were assessed by several endpoints: TEER measurement, cilia beating monitoring, LDH release, morphological observation, etc... Pro-inflammatory cytokines, IL-8 and IL-6 were used as biomarkers for discriminating these molecules. Interestingly, at sub-toxic doses, only the respiratory irritants up-regulated reversibly the secretion of IL-8 and IL-6 upon acute challenge.

**Conclusion**

As conclusion, this standardized human nasal epithelium model MucilAir™ is a promising platform for identifying the respiratory irritants and IL-8 seems to be a reliable biomarker. Additional compounds including drug compounds will be tested in the future to further validate this novel approach.