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| **Title:**  **The impact of exposure to cigarette smoke on the secreton of inflammatory mediators: assessment using human organotypic small airway epithelial cultures from five different donors**  Celine Merg1, Maica Corciulo1, Albert Giralt1, Athanasios Kondylis1, Laura Ortega1, Shoaib Majeed1, Thomas Schneider1, Anita Iskandar1, Nikolai Ivanov1, Julia Hoeng1  1 PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000 Neuchâtel, Switzerland |
| The use of modified-risk tobacco products (MRTPs) could potentially offer a better alternative to smoking (Lopez and Eissenberg, 2015)1 because they heat tobacco instead of combusting it, thus delivering an aerosol with fewer toxicants than in cigarette smoke (CS). Although clinical studies provide the most relevant data regarding the potential toxicity of MRTP aerosol exposure in humans, in vitro studies using human cells can help to uncover the associated mechanisms (cellular and molecular changes).  The commercially available human small airway culture SmallAir™ (Epithelix, Geneva, Switzerland) is an organotypic culture model reconstituted from primary human small airway epithelial cells isolated from the distal lungs of donors. Cells are cultured at the air-liquid interface (ALI) and, after approximately 3 weeks, the cultures are fully differentiated into a pseudostratified columnar epithelium exhibiting a morphology similar to their in vivo tissue counterpart comprising basal cells, club cells, goblet cells, and ciliated cells (Huang et al., 2017)2. The culture conditions at the ALI allow for direct exposure to inhalable gases (e.g., CS, aerosols, airborne particles, or nanoparticles).  Our previous study using the SmallAir™ model reported a dose-dependent secretion of pro-inflammatory mediators in response to the exposure to smoke from the scientific reference cigarette 3R4F (Iskandar, 2017)3. The present study aimed to assess the profiles of inflammatory mediators in response to 3R4F CS using five different donors (including males and females, smokers and non-smokers). The cultures were exposed for 28 minutes to two dilutions of 3R4F CS (7% and 13%) or air using the Vitrocell® 24/48 exposure system. A total of nine independent exposure experiments was conducted to increase the robustness of the observations. The basolateral media of the cultures was collected at 72 hours following exposure and a panel of several inflammatory markers was measured using Luminex® technology and Milliplex® kits (GRO, G-CSF, GM-CSF, IL-1α, IL-1β, IL-4, IL-6, IL-8, IP-10, MCP-1, RANTES, VEGF, TNF-α, MMP-1, MMP-9, sICAM-1 and TIMP-1).  Cultures obtained from the different donors presented variable basal levels of the cytokines analyzed. However, in response to 3R4F CS, a dose-dependent secretion pattern of most of the inflammatory cytokines was preserved across the different donors. Altogether, our results show that the secretion of inflammatory mediators in response to CS is highly reproducible among human organotypic small airway epithelial cultures. The results suggest that a MAP analysis is a robust endpoint to evaluate the inflammatory responses following exposure.  1.Lopez, A. A. & Eissenberg, T. 2015. Science and the Evolving Electronic Cigarette. Preventive medicine, 2015, 80, 101-106.  2.Huang et al. Establishment and characterization of an in vitro human small airway model (SmallAir).2017. Eur J Pharm Biopharm, 118, 68-72.  3.Iskandar et al. Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach. Toxicol. Res., 2017, 6, 930–946 |