Insights into pathogenic mechanisms of crystalline silica by profiling the acute response of lung epithelial cells – Focus on inflammasome activation in vitro and in vivo

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Occupational and environmental exposures to asbestos and silica are associated with the development of lung fibrosis in the forms of asbestosis and silicosis, respectively. However, both diseases display distinct pathologic presentations, likely associated with differences in gene expression induced by different mineral structures, composition and bio-persistent properties. We determined gene expression profiles and performed in-depth pathway analysis to dissect the effects of mineral exposure in the airway epithelium which may dictate early deviating molecular events that may explain the different pathologies of asbestosis versus silicosis. Our findings reveal that both minerals had potent effects on genes governing cell adhesion/migration, inflammation, and cellular stress, key features of fibrosis. Asbestos exposure was specifically associated with aberrant cell proliferation and carcinogenesis, whereas silica exposure was highly associated with additional inflammatory responses, pattern recognition and fibrogenesis. These findings illustrate the use of gene-profiling to determine early molecular events that may dictate pathological processes induced by exogenous cellular insults. A common inflammatory cascade activated in bronchial epithelial cells was the NLRP3-inflammasome. In response to silica this was found to induce secretion of IL1β, the danger molecule HMGB1 and bFGF in a particle uptake-dependent manner, and enhanced fibroblast proliferation in an autocrine fashion. Inflammasome activation furthermore occurred throughout the lungs in a rat model of silicosis, acutely upon intratracheal instillation of DQ12 silica and up to 1 year post exposure. Activation of the inflammasome was found to depend on surface reactivity as PVNO coated DQ12 markedly attenuated inflammasome-dependent readouts in vitro as well as in vivo.

Biography
N L Reynaert received her PhD cum laude in 2006 from Maastricht University on research performed in the laboratory of Prof. Janssen-Heininger at the University of Vermont, USA. She received funding from the Dutch Lung Foundation and received a prestigious personal grant from the Dutch Foundation for Scientific Research. She is the recipient of multiple awards from the European Respiratory Society and the Society for Free Radical Biology and Medicine. In 2003, she performed a sponsored fellowship in the laboratory of Prof. Brightling at the University of Leicester, UK. At the Maastricht University Medical Centre, she supervises multiple PhD projects on the topics of COPD and silicosis with an emphasis on inflammation, ageing and matrix remodeling. She has published more than 40 papers in reputed journals.

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