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Title: Silica-induced inflammasome activation in lung epithelial cells

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Body: Introduction and objectives: In myeloid cells the inflammasome plays a crucial role in innate immune defenses against pathogen- and danger-associated patterns such as crystalline silica. Respirable mineral particles impinge upon the lung epithelium causing irreversible damage, sustained inflammation and silicosis. In this study we investigated lung epithelial cells as a target for silica-induced inflammasome activation. Methods: Primary mouse tracheal epithelial cells, human bronchial epithelial cells (BEAS-2B) and primary normal human bronchial epithelial cells (NHBE) were exposed to toxic but nonlethal doses of crystalline silica over time to perform functional characterization of NLRP3, caspase-1, IL-1β, IL-33 and HMGB1. Gene expression microarray, quantitative RT-PCR, BioPlex analysis, caspase-1 enzyme activity assay, western blot techniques and cytokine specific ELISA were performed. Results: We were able to show particle uptake by lung epithelial cells, transcriptional and translational upregulation of the components of the NLRP3 intracellular platform, as well as activation of caspase-1. This activation furthermore led to maturation of pro-IL-1β to secreted IL-1β, and a significant increase in the unconventional release of alarmins such as IL-33 and HMGB1. Small interfering RNA experiments using siNLRP3 revealed the pivotal role of the inflammasome in diminished release of pro-inflammatory cytokines, danger molecules and growth factors. Conclusion: Our novel data indicate the presence and functional activation of the NLRP3 inflammasome by crystalline silica in human lung epithelial cells, which prolongs an inflammatory signal mediating a cadre of lung diseases.