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Title: Silica-induced inflammasome activation in vitro and in rat lungs

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Body: Rationale: Impingement of toxic mineral particles in the lung can cause sustained inflammation and silicosis. In this study we intended to demonstrate crystalline silica-induced inflammasome activation and the effect on fibroblast proliferation in vitro and in rat lung tissue in vivo with dependency to particle surface reactivity. Methods: siRNA mediated knock down in BEAS-2B and THP-1 cells was performed followed by 24h exposure to silica with or without surface modifications. We screened for IL-1β, bFGF and HMGB1 with ELISA. Conditioned media was added to fibroblasts. Wistar rats were instilled with PBS, 2mg Dörentruper quartz (DQ12) or 2mg polyvinylpyridine-N-oxide (PVNO) coated quartz. At days 3, 7, 28, 90, 180 and 360 after instillation, inflammasome activation was measured using immunohistochemistry. Results: We detected inflammasome dependent release of IL-1β, bFGF and HMGB1 following cristobalite and quartz treatment in vitro. Conditioned medium from BEAS-2B cells had significant impact on fibroblast proliferation. In quartz treated rats, acute inflammation was observed at 3 and 7 days. Semi-quantitative analysis revealed increased matrix deposition and fibrosis at 90, 180 and 360 days. Silicotic nodules were localized in silica exposed groups at 180 and 360 days. Levels of caspase-1 activation and IL-1β were increased in quartz versus vehicle exposed rats. PVNO-coated quartz reduced the grade of leukocyte influx and the level of NLRP3 activation. Conclusion: Our novel data indicate NLRP3 inflammasome activation by crystalline silica polymorphs in cell culture systems and in the lungs of quartz exposed rats in association with the crystalline surface reactivity.