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| **Global deletion of NLRP3 limits silica-induced inflammation and fibrosis in acute and chronic mouse models of silicosis** |
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| **Introduction/Aim:** Silicosis is an occupational lung disease, caused by chronic inhalation of crystalline silica. Uptake of silica by alveolar macrophages (AM) initiates a cycle of tissue damage, leading to increased inflammation and fibrosis. The NLRP3 inflammasome has been implicated in several inflammatory lung diseases, but it’s role in silicosis has yet to be fully defined. This study aims to characterise the role of the NLRP3 inflammasome in driving silicosis pathology, and to determine the effects of mediators released upon silica exposure.  **Methods:** Wildtype (WT) and NLRP3-/- mice received intranasal administration of PBS (control) or 2mg silica (n= 3-8/group, day 0). Levels of inflammatory cytokines, including mediators downstream of NLRP3 inflammasome activation, and cells were assessed in bronchoalveolar lavage (BAL, day 3) following acute exposure of silica. Tissue damage and collagen deposition were measured following chronic silica exposure (day 14 and 28).  **Results:** Silica increased inflammatory cell infiltration, as compared to PBS, in both WT and NLRP3-/- mice (P<0.05). In NLRP3-/- mice, silica-induced neutrophil infiltration was reduced (2.5±0.7 x104 cells/ml) compared to the WT group (4.2±0.7 x104 cells/ml), and AM number was better preserved (1.6±0.4 x104 cells/ml) in contrast to the WT group (3.4±1 x104 cells/ml). Elevated levels of BAL IL-6 and IL-18, indicative of NLRP3 inflammasome activation were reduced in NLRP3-/- mice by 51.7% And 41.6%, respectively, compared to WT mice. Silica-induced fibrosis at day 14 and 28 was notably attenuated in NLRP3-/- mice.  **Conclusion:** Global deletion of NLRP3 suppresses silica-induced inflammation and fibrosis, emphasising the critical role of the NLRP3 inflammasome in silicosis. Targeting the NLRP3 inflammasome could present a novel therapeutic approach for silicosis treatment.  **Grant Support:** MRFF Silicosis Research (MRF2006197) 2021-2024 |