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| **Deletion of NLRP3 from myeloid cells of the innate immune system reduces disease burden in a murine model of silicosis.** |
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| **Introduction/Aim:** Silicosis is an irreversible occupational disease caused by the inhalation of respirable silica particles. The NLRP3 inflammasome has been identified as a critical protein platform in generating detrimental inflammation during silicosis, however no studies to date have identified cell-specific roles for NLRP3 during silicosis pathology. Our lab has developed a novel murine myeloid specific NLRP3 conditional knockout model for the investigation of myeloid derived NLRP3 during silicosis.  **Methods:** Control (LysM-Cre) and conditional knockout (LysM-Cre x NLRP3fl/fl) mice (n=6-9 per group) were intranasally challenged with PBS (control) or silica (2mg, day 0) to induce experimental silicosis. Inflammatory and immune responses were measured in bronchoalveolar lavage fluid (BAL) at day 3. Lung fibrosis was also assessed on day 14.  **Results:** LysM-Cre Mice intranasally challenged with silica showed significant increases in pro-inflammatory cytokines such as IL-1 (7-fold increase, p<0.0001), TNF (5.3-fold increase, p<0.0001), and MCP1 (10-fold increase, p<0.0001). Additionally, infiltrating inflammatory macrophages were also significantly increased (1.3-fold increase, p=0.005).  Interestingly, LysM-Cre x NLRP3fl/fl mice demonstrated a substantial reduction prototypical inflammatory cytokine IL-12-fold decrease, p=0.0066) as well as TNF (2.1-fold decrease, p<0.0001), and MCP1 (2.9-fold decrease, p=0.0002) compared to controls. Furthermore, we identified a significant decrease in the fibrosis associated cytokine TGF (2.04-fold decrease, p=0.02). Reductions in inflammatory cytokines also lead to significantly reduced inflammatory macrophage infiltration (3.3-fold decrease p=0.03) into the lung space. Critically, we also show that reduced inflammatory burden in mice leads to reduced collagen deposition and reduced fibrotic burden of mice during the fibrotic phase of disease at day 14 (5% reduction in collagen, p=0.06).  **Conclusion:** NLRP3 deletion from the myeloid compartment of the innate immune system during silicosis may lead to reduced disease pathology. These findings further underscore the NLRP3 inflammasome as a promising novel therapeutic target for treating silicosis.  **Grant Support:** MRFF Silicosis Research (MRF2006197) 2021-2024 |