

## **Reduced responsiveness of circulating leukocytes following metal-rich particulate matter exposure**

Hulderman T, Zeidler-Erdely PC, Kashon ML, Gu JK, Young SH, Salmen-Muniz R, Meighan T, Antonini JM and Erdely A\*

NIOSH, Morgantown, WV, USA

Exposure to metal-rich particulate matter generated from welding has been linked to cardiovascular dysfunction and reduced immune competence. The aim of this study was to evaluate the molecular changes and responsiveness of circulating leukocytes following welding fume exposure. Rats were exposed to manual metal arc stainless steel welding fume (MMAW-SS) at 2 mg/rat by intratracheal instillation and harvested 4 and 24 hr post-exposure. Blood was collected and analyzed for differential changes by flow cytometry and gene expression changes by microarray and subsequent pathway analysis. In addition, anticoagulated blood was incubated for 24 hr with and without LPS stimulation utilizing the TruCulture<sup>®</sup> whole blood collection system. After incubation, supernatants were collected for protein analysis and the cellular fraction was collected for gene expression changes. Analysis of microarray data from 4hr post-exposure showed 254 network eligible genes (137-up and 117-down). The top biological category “inflammatory response” had 70 molecules of which 75% were significantly reduced. By 24 hr there were 75% fewer network eligible and altered “inflammatory response” genes. These results indicate a rapid effect on the circulating blood cell population after pulmonary exposure that was less apparent with time. *Ex vivo* stimulation with LPS of circulating leukocytes showed reduced production of CCL4, CXCL2, CXCL10 and TNF alpha protein in MMAW-SS treated rats. Cellular gene expression changes from MMAW-SS and PBS rats were similar after *ex vivo* LPS stimulation indicating effects were not at the transcriptional level. These results showed a reduced capacity of circulating leukocytes to produce inflammatory proteins in response to a secondary stimulus following a metal-rich particulate matter pulmonary exposure and provide mechanistic insight into epidemiological and experimental evidence illustrating immunosuppression following welding fume exposure.

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**\*Corresponding author:** Aaron Erdely PhD, efi4@cdc.gov