1289 Reactive Oxygen Species-induced DNA Effects of Peripheral Blood Mononuclear Cells Isolated From Rats After Pulmonary Exposure to Welding Fume

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Welding fume is a complex mixture of different potentially cytotoxic and genotoxic metals, such as Cr, Mn, Ni, and Fe. The pulmonary effects of welding fume have been well-described; however, less is known about the extra-pulmonary responses. The objective of the study was to assess the systemic effects of welding fume by examining molecular and cellular changes of isolated peripheral blood mononuclear cells (PBMC) in a rat model. Male Sprague-Dawley rats were treated by intratracheal instillation (IT) with 2.0 mg/rat of gas metal arc-mild steel (GMA-MS) and manual metal arc-stainless steel (MMA-SS) welding fume. Vehicle controls received sterile saline by IT. At 4 h, 14 h, 72 h, and 10 d, bronchoalveolar lavage (BAL) was performed to assess lung toxicity. Whole blood was collected, PBMC were isolated, and the production of reactive oxygen species (ROS) and DNA alterations in PBMC were assessed by measuring 4-hydroxylnonenal protein adduct (P-HNE) formation using fluorescence microscopy and DNA methylation and telomere length, respectively. Metal composition of the two fumes was different: MMA-SS (41% Fe, 29% Cr, 17% Mn, 3% Ni) versus GMA-MS (85% Fe, 14% Mn). BAL indicators of lung injury and inflammation were increased with MMA-SS treatment compared to other exposures at 14 h, 72 h, and 10 d after treatment. ROS generation and P-HNE adduct formation increased at 14 h in the PBMC recovered from the MMA-SS group compared to other groups. Furthermore, an increase in DNA methylation in PBMC was measured as early as 4 h after MMA-SS treatment, whereas variable responses in telomere length were observed when comparing the groups at the different time points. These findings suggest that genotoxic metals in MMA-SS fume (e.g., Cr and Ni), that are absent in the GMA-MS fume, may enhance lung toxicity, as well as generation of oxidative-stress markers and DNA alterations in PBMC.

1290 DNA Damage and Senescence Result in Epithelial Dysfunction and Pulmonary Fibrosis

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Data from human subjects has indicated Radiation Induced Lung Injury (RILI) leading to pulmonary pneumonitis and/or fibrosis occurs in 43% of all cases following radiation treatment (RT) of 15Gy or greater to the lung, with severity of injury being dependent on the lung volume irradiated and dose received. While pneumonitis is largely treatable with corticosteroid regimens, radiation induced pulmonary fibrosis (RIPF) is generally considered a life threatening, irreversible event. DNA damage as a result of radiation treatment is known to induce apoptosis, and has long been theorized to induce senescence among the surviving cell population. We have reported a decline in club cell populations and fluctuations in the immune populations in response to RT, and recent evidence suggests a decline in the type 2 alveolar epithelia as well. It is hypothesized that radiation induces persistent DNA damage and senescence in whole lung tissue, resulting in a senescence associated secretory phenotype (SASP) and type 2 epithelial population decline associated with the onset of pulmonary fibrosis. A model consisting of 18 month aged C57Bl/6J mice exposed to 12.5 Gy whole lung irradiation via a Cesium137 gamma radiation source was compared with non-irradiated age matched controls. SASP cytokines Il-1α, Il-6, CXCL-1 (KC), Surfactant Protein C (SPC) and p21 abundance was assessed in whole long tissue by rt-PCR. Changes in stromal cell populations were assessed by flow cytometry and histology, with p21 and senescence associated beta-galactosidase (SA-βgal) staining for senescence indication by histological examination. Irradiated lung displays morphology indicative of pulmonary fibrosis, and a migratory pattern of senescence expression. Whole lung tissue indicates increases in p21, decline of SPC mRNA abundance, as well as induction of SASP cytokines Il-1α, Il-6, and CXCL-1 (KC) following RT. Expression of p21 and SA-βgal is potentially linked to decline in epithelial cell subtypes within the lung which we believe to be both pro-inflammatory and pro-fibrotic. Ultimately this research may lend insight to the role senescence plays in the disruption of cell populations and signaling leading to pulmonary disease, and yield insight to therapeutic interventions for radiation induced lung injury. Supported by: R01 AI101732-01, U19AI091036, P30 ES-01247 and ES T32 07026.

1291 Gender Differences in Murine Pulmonary Responses Elicited by Nano-Crystalline Cellulose

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The emerging field of nanotechnology attracts considerable attention to special properties of nanoparticles that are utilized in a number of novel products. Cellulose-based materials have been used for centuries to manufacture different goods derived from forestry and agricultural sources. In the growing field of nano-cellulose applications, its uniquely engineered properties (e.g. mechanical, thermal, rheological and optical) are instrumental for inventive products coming to competitive markets. Cellulose nanocrystals (CNC) is a crystalline form of cellulose obtained from different cellulose sources (bacterial, alga, wood pulp, cotton, etc.) by acid hydrolysis. CNCs are already produced on a large scale as nanofillers in polymer composites, building materials, cosmetics, food, and the drug industry. The high aspect ratio and stiffness of CNC may cause similar pulmonary toxicity as carbon nanotubes and asbestos thus posing a negative impact on public health and the environment. The present study was undertaken to investigate the pulmonary outcomes induced by repeated exposure to respirable CNC. C57BL6 female and male mice were treated by pharyngeal aspiration with CNC (40 µg/mouse) two times a week for three weeks. Exposure to respirable CNC caused pulmonary inflammation and damage, cytogenic alterations assessed by frequency of bi- and micro-nucleated cells in BAL, accelerated oxidative stress, elevated TGF-β, collagen increase in lung and impaired pulmonary functions. Notably, these effects were markedly more pronounced in female compared to male mice. Moreover, gender differences in responses to pulmonary exposure to CNC were also detected at the level of global RNA expression as well as in cytokine/chemokine inflammatory reactions. Overall, our results indicate that there are considerable gender differences in responses to respirable CNC with a higher pulmonary toxicity observed in female mice.

1292 Immunomodulatory and Epigenetic Effects of Resveratrol in the Attenuation of SEB-Induced Acute Lung Injury

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Acute lung injury (ALI) is a common cause of death among people worldwide. Recently, plant-derived compounds such as resveratrol (RES), which has antioxidant and anti-inflammatory properties, has been explored as a possible treatment against inflammatory diseases. In this study, we explored the role of RES in suppressing inflammation induced by an inhaled super-antigen, staphylococcal enterotoxin B (SEB). To this end, mice were pretreated with RES or vehicle and the ALI was induced by dual-dose administration of SEB. All SEB exposed mice pretreated with vehicle succumbed within 120 hours, while 100% of mice pretreated with RES survived. CD3, CD4, CD8 and NK+CD3 lymphocyte subsets in the lungs of SEB-exposed mice treated with vehicle were significantly higher than RES treated mice. Pulmonary function was evaluated and showed impairment in the vehicle treatment group that was restored with RES treatment. Histopathological analysis and the vascular leak test demonstrated that SEB caused a statistical increase in infiltrating cells into lung parenchyma, likely explaining the clinically observed dyspnea and anoxia. Interestingly, cell cycle analysis revealed that infiltrating cells from the lung were paused in G2/M phase in both mice groups. Total RNA was extracted from lung infiltrate for microRNA (miRNA) microarray and several miRNAs were altered upon RES treatment. Downregulation of miR-193a-3p, which targets TGF-beta was confirmed by real-time PCR. Importantly, TGF-beta upregulation is known to result in increased T-reg cells and reduced activated CD4+ cells, as seen with RES treatment. We conclude that RES treatment protects against super-antigen induced inflammation by immobilizing T-cells and thereby decreasing vascular endothelial dysfunction at the site of exposure, possibly by acting through miRNAs. (Supported by NIH grants P01AT003961, R01AT006888, R01ES019313, R01MH094755, P20RR032684 and VA Merit Award BX001357).

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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