In conclusion, unlike the current opinion, silica alone can induce metabolic changes in RAW macrophages that eventually determine chronic inflammation and silicosis.

2551 Lung Fibroblasts from Idiopathic Pulmonary Fibrosis Patients Produce an Oxidizing Extracellular Redox Potential

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Idiopathic pulmonary fibrosis (IPF) is associated with increased deposition of extracellular matrix proteins, and lung fibroblasts are responsible for producing these pro-fibrotic proteins. One of the signals that evokes pro-fibrotic gene expression is a shift in the extracellular cysteine/cystine redox potential (E_h(Cys/CySS)) toward more positive (more oxidizing) potentials. Recently, we found that mouse lung fibroblasts can regulate their own extracellular E_h(Cys/CySS) and that changes in the activity of the CySS transporter Slc7a11 can change the value at which E_h(Cys/CySS) is maintained. Our hypothesis is that human lung fibroblasts from patients with IPF express low levels of SLC7A11 and produce an oxidizing extracellular E_h(Cys/CySS). IPF fibroblasts were isolated from explants of 6 IPF patients receiving lung transplant. Non-IPF fibroblasts were isolated from relatively normal lung tissues adjacent to cancerous tissues of 6 lung cancer patients. SLC7A11 mRNA levels were measured by qPCR. Concentrations of Cys, CySS, glutathione (GSH), glutathione disulfide (GSSG) and mixed disulfide (CySSG) were measured by HPLC. Nernst equation was used to determine the redox potentials. The data showed that extracellular E_h(Cys/CySS) was more oxidized for lung fibroblasts from IPF patients than those from non-IPF donors. Oxidation of E_h(Cys/CySS) in IPF fibroblasts was not due to decreased expression of SLC7A11. However, higher SLC7A11 expression was correlated with more reduced extracellular E_h(Cys/CySS) and more reduced intracellular E_h(GSH/GSSG) in non-IPF fibroblasts, but not in IPF fibroblasts. Therefore, SLC7A11-dependent regulation of extracellular and intracellular redox environments is lost in lung fibroblasts from IPF patients, suggesting that SLC7A11-independent mechanisms are responsible for aberrant redox regulation in this important effector cell of pulmonary fibrosis.

2552 Inhalation Co-exposure to Ultrafine Carbon and Ozone Leads to Significant Pulmonary and Systemic Oxidative Stress

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Particles and gases are integral components of ambient air pollution and both contribute significantly in adverse health outcomes. Recent epidemiologic data indicates that possible synergistic interactions between these components mediate the adverse phenotypes. Mechanistically, gaseous components can modify the particle surfaces and can reach distal portions of the lung, owing to the deeper penetrability of ultrafine particles. We hypothesize that ultrafine particles of carbon black (CB) and ozone (O_3) co-exposure will lead to significantly greater oxidative stress response in the lungs, heart and liver compared with individual/single toxicant exposures. We performed rodent (C57Bl/6J mice) whole-body inhalation exposures (air, CB, O_3 or CB+O_3) and studied acellular and cellular bimolecular free radical production by immuno-spin trapping. Mice were exposed to 2.0±0.02 ppm O_3 and/or 10±0.6 mg/m^3 CB for 3 hours (16 µg particle deposited dose). Aerosol mobility (140±2 nm), and aerodynamic (84±1 nm) diameters were measured by scanning mobility particle analyzer (SMPS 3938) and an electrical low-pressure impactor (ELPI+). Fourier transformed infrared (FTIR) spectroscopy demonstrated significant alteration in particle surface functional group composition after interaction with O_3. Ferric reducing ability of serum (FRAS) assay demonstrated significantly greater acellular oxidative potentials for co-exposure aerosol. A significantly greater increase in pulmonary and distal organ free radical production, xanthine oxidase activity and gene expression occurred after co-exposures compared with single exposures. In conclusion, our studies confirm interaction of gaseous and particle components of air pollution. By demonstrating distal organ oxidative stress response after pulmonary exposure, we describe a potential pathophysiologic mechanism for cardiovascular and hepatic dysfunction by air pollution exposure. Further mechanistic studies are underway to elaborate these findings using organoids and disease animal models. *Funding: NIH/NIGMS U54GM104942-03 (SH), NIH R01ES015022 (TRN), AHA 19TPA34850089, NIH HL 136383 (EK).*

2553 Glucocorticoids Regulate *SLC7A11* Expression and Sensitivity to Oxidative Stress

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SLC7A11 encodes an antiporter that exchanges glutamate for cystine. Cystine is a precursor to the antioxidant glutathione, and therefore, SLC7A11 activity increases cellular antioxidant capacity. *SLC7A11* is regulated by multiple stress responsive pathways, with altered expression implicated in multiple diseases. Using publicly available data we examined potential regulatory regions and hypothesized that the transcription factor (TF) glucocorticoid receptor (GR) represses *SLC7A11* expression. To test this, we treated A549 cells with ± 3µM mifepristone (MIF), a GR antagonist, for 24 hrs, then treated cells with ± 100nM dexamethasone (DEX), a GR agonist, for an additional 24 hrs. qRT-PCR measured expression of *SLC7A11* relative to a housekeeping gene, and the fold change relative to vehicle control was calculated. Treatment with DEX significantly repressed *SLC7A11* expression (0.43 ± 0.013, p=0.0001) and this was blocked by pre-treatment with MIF (0.90 ± 0.05), suggesting that DEX-mediated repression of *SLC7A11* is specific to GR. We then tested whether cells exposed to DEX are more susceptible to oxidative stress. A549 cells were treated with 100nM DEX (or vehicle) for 24 hours and then exposed to a wide concentration range of an inducer of oxidative stress, tert-Butyl hydroperoxide (TBOOH), or vehicle, and assessed for viability. Cells treated with DEX were more susceptible to TBOOH (+DEX EC50: 81.1µM, 0 DEX EC50: 230.9µM). qRT-PCR and TBOOH cytotoxicity experiments were repeated in HELA cells and rat astrocytes and the trends were consistent. Finally, we explored the potential *cis*-regulatory regions we identified at the *SLC7A11* locus using luciferase reporter assays; A549 cells were transfected with reporter constructs containing either the *SLC7A11* promoter, or the *SLC7A11* promoter plus *cis*-regulatory regions in intron 9 (I9) or intron 2 (I2). Following transfection, cells were treated with MIF and/or DEX in an exposure paradigm as described above. Repression was primarily mediated by the *cis*-regulatory regions in the promoter and I2. Further, we think that the repression in these regions is a result of GR tethering to another stress responsive TF, NRF2, and binding to an antioxidant response element. In summary: GR represses *SLC7A11* via *cis*-regulatory regions in the promoter and I2, likely via tethering to the TF NRF2. Repression of *SLC7A11* results in less exchange of glutamate for cystine, and this renders cells more susceptible to oxidative stress.

2554 Stat3 as a Novel Methylmercury-Induced Antioxidant Mechanism

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Methylmercury (MeHg) is an environmental pollutant that affects the developing and the mature central nervous system. Despite extensive research over the past decades, the molecular mechanisms mediating MeHg neurotoxicity have not been fully elucidated. Oxidative stress, impairment of the antioxidant defense and disruption of the calcium homeostasis are some of the mechanism associated with MeHg toxicity. The induction of nuclear factor erythroid 2-related factor 2 (Nrf2) and its role activating antioxidant response under MeHg-induced oxidative injury focus the attention of the scientific community as a target to counteract MeHg toxicity. Recent studies show that the Nrf2 signaling pathway is insufficient to prevent MeHg damage but there may be other protective mechanisms. The signal transducer and activator of transcription 3 (STAT3) has a pivotal role in cell growth and survival. Some studies also showed that STAT3 plays a role controlling redox homeostasis, preventing oxidative stress by a mechanism that includes modulation of nuclear genes encoding for electron transport complexes (ETC) and antioxidant enzymes. STAT3 also acts by non-classical mechanism, via mitochondria localization where interacts with complex I, increasing membrane potential and promoting ATP synthesis. All these features make STAT3 a plausible mechanism to prevent MeHg toxicity, in conjunction or as alternative to Nrf2 signaling. Here, using an immortalized neuronal hypothalamic GT1-7 cell line we tested if MeHg is able to induce the STAT3 signaling pathway. Our data show that MeHg exposure is associated with upregulation of STAT3-Y705 phosphorylation, inducing its nuclear translocation and regulating STAT3 associated gene expression. In addition, MeHg is also able to induce the phosphorylation at STAT3-S727, which is implicated in its mitochondrial localization. Moreover we found that the inhibition of STAT3 phosphorylation exacerbates MeHg toxicity increasing oxidative stress and mortality. Overall, we show that MeHg is able to induce both classical (nuclear) and non-classical (mitochon-

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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 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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