PS 1584 Temporal Evaluation of Multicompartment Molecular Signaling following an Inhalation Exposure to Metal-Rich Particulate Matter

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Adverse cardiovascular effects after particulate inhalation exposures have been reported; however, the mechanisms involved are largely unknown. For mechanistic insight, we investigated global transcriptional alterations in the target organ (lung) as well as several extrapulmonary tissues (heart, aorta, whole blood cells) following inhalation (40 mg/m3 for 3 h/d for 5 d a week for 10 d) to stainless steel welding fume. Tissues were collected 4 h and 28 d post-exposure, RNA was isolated and microarray results were analyzed using Ingenuity Pathway Analysis for pertinent biological and molecular networks associated with effects. Utilizing the upstream regulator (i.e. transcription factors, cytokines, growth factors) analysis, the lung had 285, blood cells 30, aorta 39, and heart 32 significantly altered mediators 4 h post-exposure. There was a graded decline in the total mediators at 28 d with the lung decreasing by 3%, blood cells 37%, aorta 77% and heart 100%. When examining the connectivity of signaling at 4 h, 90% of the upstream regulators in the blood cells were reflective of the lung response, 90% in the aorta, and 44% in the heart. Specific mediators of interest in the aorta (Mt2, Sele, Hspa1b, Vcam1) predictive of adverse vascular effects were increased. Mitochondrial dysfunction was the top canonical pathway in the heart with the top three signaling networks centering on altered energy metabolism. PPARGC1A, a transcription factor regulating mitochondrial biogenesis and function and induced by oxidative stress, was increased and linked to many of the altered cardiac upstream regulators and genes associated with mitochondrial dysfunction. In conclusion, systemic signaling, suggestive of oxidative stress-mediated cardiovascular dysfunction, was strongly reflective of the ongoing pulmonary response although the altered signaling was not sustained compared to the lung.

PS 1585 Toxicity of Mineral Dusts and a Proposed Mechanism for the Pathogenesis of Particle-Induced Lung Diseases

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Humans will set foot on the moon again. The lunar surface has been bombarded for 4 billion years by micrometeoroids and cosmic radiation, creating a layer of fine dust having a potentially reactive particle surface. To investigate the impact of surface reactivity (SR) on the toxicity of particles, and in particular, lunar dust (LD), we ground 2 Apollo-14 LD samples to increase their SR and compare their toxicity with those of unground LD, TiO2 and quartz. Intratracheally instilled at 0, 1, 2.5, or 7.5 mg/rat, all dusts caused dose-dependent increases in pulmonary lesions, and enhancement of biomarkers of toxicity assessed in bronchoalveolar lavage fluids (BALF). The toxicity of LD was greater than that of TiO2 but less than that of quartz. Three LDs differed 14-fold in SR but were equally toxic; quartz had the lowest SR but was most toxic. These results show no correlation between particle SR and toxicity. Often pulmonary toxicity of a dust can be attributed to oxidative stress (OS). We further observed dose-dependent and dust-cytotoxicity-dependent increases in neutrophils. The oxidative content per BALF cell was also directly proportional to both the dose and cytotoxicity of the dusts. Because neutrophils are short-lived and release of oxidative contents after they die could initiate and promote a spectrum of lesions, we postulate a general mechanism for the pathogenesis of particle-induced diseases in the lung that involves chiefly neutrophils, the source of persistent endogenous OS. This mechanism explains why one dust (e.g., quartz or nanoparticles) is more toxic than another (e.g., micrometer-sized TiO2), why dust-induced lesions progress with time, and why lung cancer occurs in rats but not in mice and hamsters exposed to the same duration and concentration of dust.

PS 1586 Fine Particles of Mexico City As a Potential Adjuvant in an Allergic Asthma Model

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Air pollution represents a serious worldwide health problem, especially in megacities like Mexico City. Several contaminants, as particulate matter, may contribute to asthma development, which is a chronic airway disease characterized by inflammation and reversible obstruction. Some studies in allergic asthma models have found that PM can induce exacerbations depending of sources and PM composition. Our aim was to determine if whether exposure to fine particles (PM2.5) of Mexico City can generate asthma attacks in a guinea pig model. Animals were sensitized to ovalbumin (OVA as allergen) with or without AlOH3 (as adjuvant) and exposed to filtered air (FA) or PM2.5 (daily 5h/3days), using an aerosol concentration system in the north of Mexico City (CINVESTAV-Zacatenco). Plethysmographic studies were conducted before and after OVA challenge to obtain an airway resistance index. Animals were euthanized and bronchoalveolar lavage was performed in order to determine the immunological profile using ELISA multiplex assays (specific IgG, OVAIgG1, OVAIgE, CC16 and TH1/TH2 cytokines). Lung samples were recovered for histology. OVA challenge induced bronchospasm in all the sensitized with or without AlOH3 animals that was exacerbated by PM2.5 exposure. Immunological and lung damage biomarkers increased statistically in sensitized animals even in those without adjuvant but exposed to FP. Mucous metaplasia was observed in asthmatic and asthmatic exposed to PM2.5. Our results suggest that PM2.5 of Mexico City can cause asthma *de novo* and enhance the attacks in the allergic guinea pig asthma model acting as a potential adjuvant. Author is a Scholarship holder CONACYT/CVU326096 (Posgrado en Ciencias Biológicas, UNAM). Study supported by: SECITI 042/2013.

PS 1587 Effects of Chemical Composition on the Activation of TRPA1 by Diesel Exhaust Particulate Materials

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Diesel exhaust particulates (DEP) are a common source of fine-particulate air pollution (PM). Over the past decade many changes have been made to diesel formulation and emissions standards in recognition of the impact DEP has on the environment and human health. Inhalation of DEP can cause irritation to the nose and throat, pulmonary inflammation, exacerbation of asthma, and promote chronic pulmonary diseases. This appears to be in part, due to its ability to activate transient receptor potential ankyrin-1 (TRPA1). The purpose of this study was to evaluate the relationship between chemical composition of DEP collected from various sources (poorly functioning on road truck ("black smoker"), industrial fork lift (NIST), DEP recovered during diesel filter regeneration, and biodiesel) and activation of TRPA1. Ca++ flux was quantified in TRPA1 over-expressing HEK-293 cells: "black smoker" DEP was the most potent TRPA1 agonist followed by NIST, Filter, and biodiesel PM. Chemical analysis of DEP components by HPLC, LC/MS, and GC/MS revealed a correlation between DEP potency and the abundance of perinaphthenone, benzoquinone, and 3,5-ditertbutylphenol in ethanol extracts of DEP. The unique chemistry of the DEP was further demonstrated utilizing indiscriminant GC/MS analysis and principal component analysis (PCA). The mechanism of TRPA1 activation was also investigated. TRPA1 activation by "black smoker" and NIST were primarily attributable to electrophiles, whereas Filter activated primarily via the menthol-binding site. Despite the unique chemical properties of these DEP, we did not observe differences in their ability to alter the expression of commonly studied genes including IL-8, in A549 lung cells, which naturally expresses TRPA1, when applied at an equivalent extract mass concentration. These studies show that the chemical composition of DEP is less of a factor for determining how cells respond to TRPA1 agonists, and suggest that multiple cellular pathways are probably involved in shaping cellular responses to DEP. Support: ES017346

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