

the control group from the treated group over the time series in hierarchical gene clustering analysis. Furthermore, 4 genes from these two sets of significant genes, Cdc99, Msx2, Nos2 and Wif1, showed significant mRNA expression perturbations at both time points. It was also found that the expression changes of these 4 overlapped genes at 7-days post-exposure were attenuated at 56-days post-exposure. The results of MWCNT exposure-induced gene expression changes reveal the characteristics of carcinogenesis and may indicate the association of MWCNT exposure with lung cancer progression. These results also indicate that MWCNT exposure may induce the alteration of several key carcinogenesis-related signaling transduction pathways. Taken together, the results obtained from this study indicate the potential lung carcinogenic effects of MWCNT exposure in humans and could potentially be used for the medical surveillance for MWCNT workers.

PS 1186 MULTI-WALLED CARBON NANOTUBE INSTILLATION IN C57BL/6 MICE INDUCES CHANGES IN PULMONARY FUNCTION.

P. Katwa¹, A. Aldossari¹, S. C. Hilderbrand¹, C. J. Wingard², D. M. Walters² and J. M. Brown¹. ¹Pharmacology & Toxicology, East Carolina University, Greenville, NC and ²Physiology, East Carolina University, Greenville, NC.

As the production and use of nanomaterials increases, the potential for human exposure also increases thereby placing greater emphasis on potential health hazards. Multi-walled carbon nanotubes (MWCNT) in particular, are widely used for their versatility in many disciplines due to their unique physical and chemical properties. The purpose of this study was to examine the long-term pulmonary inflammatory and fibrotic effects of MWCNT at 7, 30, 60 and 90 days post-exposure. Inflammatory and fibrotic responses in lungs of C57BL/6 mice following MWCNT instillation were assessed by cytokine expression, bronchoalveolar lavage cell counts, collagen content, pulmonary function testing and histological assessment. Mice instilled with MWCNT (100 µg) exhibited increased expression of pro-inflammatory and pro-fibrotic cytokines, which were associated with increased infiltration of macrophages, neutrophils, eosinophils and lymphocytes up to 60 days post-exposure. In addition, pulmonary function testing demonstrated an increase in the area within the pressure-volume loops (PV loops) for MWCNT treated mice compared to vehicle control indicating a change in lung hysteresis. These findings corroborate histological data exhibiting increased granuloma formation and development of fibrosis up to 90 days associated with increased collagen content in lung tissue of C57BL/6 mice instilled with MWCNT. These data indicate that exposure to MWCNT results in adverse pulmonary effects, including increased pulmonary inflammation, fibrosis and compromised lung function. This work supported by NIH RO1 ES019311 (JMB) and ES016246 (CJW).

PS 1187 CARBON NANOTUBES INDUCE APOPTOSIS RESISTANCE THROUGH FLICE-INHIBITORY PROTEIN.

V. Pongrakhananon¹, Y. Lu¹, L. Wang², T. Stueckle², S. Luanpitpong¹ and Y. Rojanasakul¹. ¹West Virginia University, Morgantown, WV and ²National Institute for Occupational Safety and Health, Morgantown, WV.

Our studies have shown that chronic exposure to single-walled carbon nanotubes (SWCNT) induces apoptosis resistance and malignant transformation of human lung epithelial cells. Since resistance to apoptosis is a foundation of neoplastic evolution and selection of malignant transformed phenotype, we investigated the apoptosis pathway underlying the resistance its mechanisms to aid the understanding of SWCNT-induced carcinogenesis. As compared to passage-matched control cells, SWCNT-transformed BEAS-2B cells exhibited resistance to apoptosis induced by death ligands, e.g., tumor necrosis factor-α and Fas ligand, but not by inducers of mitochondria-mediated apoptosis, e.g., antimycin A and cisplatin, suggesting death receptor pathway as the primary pathway of defective apoptosis in SWCNT-transformed cells. The results were confirmed using caspase specific inhibitors and caspase activity assays. DNA microarray and Western blot analyses of key apoptosis-regulatory proteins in the transformed cells revealed FLICE-inhibitory protein (FLIP) as an important target of regulation by SWCNT. Overexpression of FLIP increased apoptosis resistance of the cells, whereas RNAi knockdown of FLIP reversed the apoptosis resistance of cells in response to death ligands. Together, our study demonstrated a novel mechanism of apoptosis resistance induced by chronic exposure to SWCNT in human lung epithelial cells and identified FLIP as a key regulator of apoptosis avoidance that contributes to the development of malignant transformed phenotype. [This work is supported by the NIH grant R01-HL095579]

PS 1188 POTENTIAL CARCINOGENICITY OF CARBON NANOTUBES.

Y. Rojanasakul¹, Y. Lu², S. Luanpitpong², V. Castranova¹, V. Pongrakhananon² and L. Wang¹. ¹National Institute for Occupational Safety and Health, Morgantown, WV and ²West Virginia University, Morgantown, WV.

Carbon nanotubes (CNT) have increasing been used for wide applications with a potential for human exposure. Concerns about the potential carcinogenicity of CNT have been raised since CNT exhibit a bio-persistence and a fibrous morphology similar to asbestos which is a known carcinogen. However, there is neither clear knowledge nor a practical method to assess this potential. In this study, we developed an in vitro chronic exposure model combined with in vivo xenograft model to address these needs. Non-tumorigenic human lung epithelial BEAS-2B cells were continuously exposed to a sub-cytotoxic concentration (0.04 µg/ml or 0.02 µg/cm² exposed area) of single-walled CNT (SWCNT) in culture. Phenotypic changes were observed in SWCNT-treated cells 20 weeks post-exposure such as formation of cell mounds and accelerated cell growth. SWCNT-treated cells were subsequently analyzed for malignant properties including colony formation, cell migration and invasive properties. Significant positive results were observed from SWCNT-treated cells in all above studies compared to passage-matched control cells. In vivo tumorigenesis study was performed by subcutaneously injecting the transformed cells into nude mice. Consistent with the in vitro cell transformation results, the in vivo results showed large tumor formation at the injection site in mice receiving SWCNT-transformed cells, whereas mice receiving control cells showed no tumor formation. These studies indicate that long-term/low dose exposure of human lung epithelial cells to SWCNT induced malignant transformation of the cells which induced tumor formation in vivo. These results suggest a potential carcinogenic effect of SWCNT. The described cell model system could potentially be used as a predictive model for carcinogenicity testing of nanomaterials. [This work was supported by the NIH Grant R01-HL076340]

PS 1189 PULMONARY EXPOSURE TO CARBONACEOUS NANOPARTICLES AFFECTS LOCAL AND SYSTEMIC IMMUNITY.

A. Tkach¹, E. Kisin¹, A. R. Murray¹, G. V. Shurin², M. R. Shurin², S. H. Young¹, A. Star², B. Fadeel³, V. E. Kagan² and A. A. Shvedova¹. ¹PPRB, NIOSH, Morgantown, WV, ²University of Pittsburgh, Pittsburgh, PA and ³Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

Numerous studies have focused on the toxicity associated with nanoparticle (NP) exposure. The results of studies on rodents have demonstrated that NP are capable of inducing inflammation, granulomas, fibrosis, and mutagenicity found in the lungs. However, immunologic effects of inhaled nanoparticles remain largely unexplored. In the current study, we evaluated the inflammatory response in the lung and systemic immune effects induced by pulmonary exposure to 40-120 µg/mouse of pristine (C₆₀) or functionalized (C₆₀-TRIS) fullerenes or single-walled carbon nanotubes (SWCNT). We demonstrated that pharyngeal aspiration of the studied NP caused inflammation and pulmonary damage as evidenced by accumulation of PMNs, changes in lung permeability and cell damage. In addition, NP stimulated release of pro-inflammatory and regulatory cytokines in the lung. Further, local inflammatory response was translated into suppressed systemic immunity as evidenced by 25% decrease in proliferation of splenic T cells stimulated by allogeneic dendritic cells (DC). To investigate possible mechanisms of compromised systemic immunity, we evaluated the ability of NP to directly affect stimulatory/polarizing activities of conventional DC (cDC) towards T cells *in vitro*. Exposure of cultured cDC to NP resulted in an impaired ability to stimulate T cells in an allogeneic MLR assay (up to 4-fold suppression). This effect was due to neither altered expression of CD80, CD86 or MHCII on DC as exhibited by DC phenotyping, nor by increased production of IL-10. Thus, mechanisms of altered systemic immunity in treated mice might be, at least in part, due to the direct effects of NP on cDC. Overall, our data suggest that NP affect and trigger both local and systemic immune responses in mice.

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PS 1190 PULMONARY RESPONSE OF CIGARETTE SMOKE-EXPOSED MICE TO CARBON NANOPARTICLES.

C. Gairola¹, S. Han¹ and D. Bhalla². ¹Graduate Center for Toxicology, University of Kentucky, Lexington, KY and ²Wayne State University, Detroit, MI.

Concurrent or sequential exposures to more than one air pollutant can potentially affect pulmonary toxicity. Carbon nanoparticles when instilled into the lungs of mice induce an acute pulmonary response. To determine if such a response is influ-

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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