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Malignant transformation and toxicogenomic responses of human lung cells to chronic exposure of carbon nanomaterials

Accumulating studies reported that inhaled carbon nanotube (CNT) exposure results in elevated risk for interstitial lung diseases and persistence within exposed lung tissues. This raises a major concern about the long-term human health risks associated with chronic pulmonary CNT exposures, especially potential carcinogenicity of CNT which exhibits a fibrous morphology similar to asbestos, 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 to address this knowledge gap. We conducted subchronic *in vitro* exposures of dispersed single-walled CNT (D-SWCNT), multi-walled CNT (D-MWCNT) and crocidolite asbestos (ASB) to human small airway epithelial cells (SAEC). Ultrafine carbon black (D-UFCB) and dispersant-only exposed cells (DISP) served as negative controls. SAEC were exposed to 0.02μg/cm^2 of the particles for 25 weeks and evaluated for cancer cell phenotype. Next, mRNA samples were subjected to whole genome microarray and rtPCR analyses for toxicogenomic evaluation. Differentially expressed genes were uploaded to Ingenuity Pathway Analysis to identify novel mechanisms promoting neoplastic transformation. Our results showed that both D-SWCNT and D-MWCNT-treated cells exhibited typical malignant transformation properties, such as increased proliferation, migration/invasion, anchorage-independent cell growth and angiogenesis compared to controls. Both D-SWCNT and D-MWCNT cells expressed significant changes in genes associated with cell death, movement, proliferation and cancer. Top ranked pathway along with Western blot analyses identified several altered signaling pathways and transcription factors associated with oncogenesis. These results indicate that long-term/low-dose exposure of human lung epithelial cells to D-SWCNT and D-MWCNT induced neoplastic transformation of the cells which suggests a potential carcinogenic effect of the nanomaterials. The described cell model system could potentially be used as an *in vitro* predictive screening test of other nanomaterials for potential carcinogenicity. Phenotypic anchoring of toxicogenomic response to neoplastic cell transformation following *in vitro* subchronic nanomaterial exposure can potentially serve to identify novel mechanisms of action and provide human health risk assessment data.

Keywords: Carbon nanotubes; Microarray analysis; Tumorigenesis; Lung; Cell

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Biography

Yon Rojanasakul is Robert C. Byrd Distinguished Professor and Program Leader at the West Virginia University Mary Babb Randolph Cancer Center. He is also a guest scientist at the National Institute for Occupational Safety and Health, USA. He received his Ph.D. in Pharmaceutical Sciences from the University of Wisconsin at Madisonin 1989 and has since worked as a full-time faculty member at West Virginia University. Dr. Rojanasakul's research is in the areas of occupational and environmental toxicology, nanotechnology and molecular carcinogenesis. His research focus is on cellular and molecular mechanisms of lung fibrosis and carcinogenesis induced by respirable dusts, nanomaterials, and heavy metals. He has published over 170 peer-reviewed research articles in reputable journals.