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Clearing the Hurdles for Nanotechnology: In vivo inhalation effects

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INTRODUCTION: Nanoparticles of many types have been created for industrial and medical applications. Among these nanoparticles, single-walled carbon nanotubes (SWCNT) are of high interest for their physicochemical properties and application in electronics, drug delivery and other areas. With the rapid expansion in SWCNT-based new technologies, a full understanding of their safety and risks for human exposure must be considered. Because of the potential human risk of nanoparticle exposure we have developed an animal model to study the effects of nanoparticle exposure on lung tissue. Using this rat model we hypothesized that an acute nanoparticle exposure would result in an inflammatory response in lung tissue. **METHODS:** Particle instillation (intratracheal under direct visualization) of 50 µL pediatric surfactant containing 500 micrograms SWCNT (or surfactant alone) was performed in 32 rats to date. Pulmonary histology and biochemical measures on bronchoalveolar lavage (BAL), pleural fluid, serum and lung cells was quantified. **RESULTS:** Very early (<30 minutes) eosinophilia developed in lung tissue following SWCNT instillation. Innate immune system sterile response, or Damage Associated Molecular Patterns (DAMPs) protein was released. Our dose proved sterile, <0.03 EU LPS, showing the effect was damage-induced not pathogen-induced. High mobility group box protein-1 (HMGB1), a nuclear chaperone and prototype DAMP was elevated (ELISA) following SWCNT exposure. A second DAMP, heatshock protein 70 (HSP-70), a cytoplasmic chaperone, was also quantified by ELISA. The response OF HSP-70 over time is similar to HMGB1. Western blots performed on time-harvested lungs exposed to SWCNT demonstrated a receptor for advanced glycation end products (RAGE), with a strong peak at 3 hours after pulmonary exposure. The inflammatory cytokine TNFα appeared in lung tissue and bronchial alveolar lavage (BAL) at 30 minutes, with the same timing as the HMGB1 and HSP-70 release. Flow cytometry of type II pneumocytes and pulmonary macrophages from SWCNT-exposed rats demonstrated secondary DAMP receptors. A potential chronic effect was noted at one month. HMGB1 and HSP-70 peaked acutely at approximately 24 hr and then slowly decreased at 1 to 2 weeks. At 1 month, however, a new increase was seen. **CONCLUSIONS:** The hydrophobic SWCNT, important industrial components, form bundles and fibers in the hydrophilic lung, creating an immediate cellular inflammatory response, measurable cellular necrosis and very rapid chemokine release. Early data suggests the potential for chronicity.