Respiratory Toxicity of Inhaled Carbon Nanotubes

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The unique physical characteristics of nanosized materials have raised concerns about possible adverse effects on human health. However, the toxicity of inhaled nanomaterials has not been investigated and, therefore, remains unclear. Carbon nanotubes are manufactured for a wide variety of applications in material sciences and electronics. We discovered that single-walled carbon nanotubes delivered in a one-day exposure to Sprague-Dawley rats by intratracheal instillation for six hours at 100 mg/m³ caused increases in levels of (1) the pro-fibrogenic cytokine platelet-derived growth factor (PDGF) in rodent lung, and (2) the interstitial pulmonary fibrosis and unique intercellular carbon structures composed of nanotubes that form stable bridges between lung macrophages. We also discovered that PDGF is important in airway fibrosis associated with asthma, where it is regulated by interleukin-13 (IL-13). More recently, we discovered that multi-walled carbon nanotubes, delivered to C57BL6 mice by nose-only inhalation for six hours at 100 mg/m³, exacerbated airway fibrogenesis and caused increased levels of PDGF and monocyte-chemotactic protein-1 (MCP-1) in the lungs of mice. Moreover, inhaled multi-walled carbon nanotubes migrated to the pleura and caused pleural inflammation and fibrosis. It is exceedingly important to assess the biocompatibility of carbon nanotubes, especially in individuals with pre-existing respiratory disease such as asthma.

Our central hypothesis was that carbon nanotubes exacerbate IL-13-induced PDGF production and fibrosis in asthma through two combinatory physico-chemical properties: trace metal catalysts and high specific surface area. We further postulated that the unique fiber-like shape of nanotubes contributes to (1) the formation of intercellular carbon nanotube structures that bridge macrophages and (2) the potential for nanotube biopersistence in the lung. Our work will determine whether or not carbon nanotubes delivered by aspiration or inhalation exposure enhance PDGF production and airway fibrosis in a mouse model of asthma induced by ovalbumin. We will also elucidate the intracellular signaling pathways through which nanotubes increase PDGF production by lung cells in vitro. In addition, our work will determine whether or not metal nanoparticles (e.g., cobalt, nickel, iron) used as catalysts in the synthesis of carbon nanotubes cause increased PDGF production and fibrosis in normal and ovalbumin-challenged mice. We will also determine whether or not metal catalysts stimulate oxidant-dependent intracellular signaling that enhances IL-13-induced PDGF production in lung cells. Further experiments will be undertaken to determine whether carbon nanoparticles of different mean diameters in the absence or presence of metal nanoparticles cause increased PDGF production and fibrosis in normal and ovalbumin-challenged mice. We will also test the hypothesis that increasing surface area, alone or with metal catalysts, determines whether carbon nanotubes stimulate cell signaling and PDGF production in cultured mouse and human lung fibroblasts. Finally, we will investigate the mechanisms through which nanotubes form intercellular bridges in the lung and determine whether these structures cause nanotube biopersistence in the lung. In the last year of the project, we examined mesothelial interactions of these particles in rodent lungs.

Implications: Nanoparticles of various kinds, including nanotubes, have many uses. However, the implications of inhalation exposures are not adequately understood. This research directly examined the pulmonary toxicity of inhaled carbon nanotubes and the interaction of these particles with known physiological pathways in the lung. This information is essential to sound decision making based on known responses to these particles, rather than basing decisions on unfounded concerns that stem from responses to high doses in cellular systems or in the lungs.

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