Chapter 56
Toxicological Effects of Carbon Nanotubes

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ABSTRACT

The rapidly evolving field of nanotechnology offers many potential societal and economic benefits. Carbon Nanotubes (CNTs) are one of the most widely produced engineered nanomaterials and have diverse applications in engineering, electronics, and medicine. They have also been extensively investigated for their toxicological properties. Studies with rodents indicate that CNTs can cause lung fibrosis or granuloma formation, exacerbate pre-existing respiratory disease, cause injury to the sensitive pleural lining of the lungs, and have systemic immunosuppressive effects. CNTs have also been reported to cause genotoxic effects on cultured cells. The fiber-like structure of CNTs has led to comparisons with asbestos fibers; yet the debate over whether CNTs cause mesothelioma remains highly controversial, and evidence thus far is lacking. The aim of this chapter is to overview the evidence in rodent models that CNTs cause lung disease and to discuss the potential of CNTs to cause adverse immune, fibrogenic, or carcinogenic effects in humans as a result of occupational, consumer, or environmental exposure.

INTRODUCTION

Carbon nanotubes (CNTs) are proto-typical engineered nanomaterials that possess superior strength with minimal weight. CNTs also can be easily functionalized at the atomic level to enhance their properties for use in electronics, engineering, and biomedicine. While promising for many uses, the length and high tensile strength of CNTs also make them a potential risk for lung diseases and as well as other systemic sites of injury [Bonner 2010a]. The most likely route for human exposure is inhalation. A growing number of studies using rats or mice show that CNTs delivered to the lungs cause interstitial lung fibrosis, granuloma formation, or fibrogenic reactions at the pleura [Bonner 2011]. CNTs also exacerbate pre-existing respiratory disease and cause systemic effects in other organ systems such as heart and spleen [Thompson et al., 2013]. While rodent studies indicate that CNTs cause adverse pulmonary and systemic effects, there is currently no epidemiologic data demonstrating that CNTs cause disease

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in humans. This is likely due to the infancy of the nanotechnology industry and the long latency time for chronic lung diseases in humans. A major goal for investigators in the field of nanotoxicology is to better understand the adverse effects and mode of action for engineered nanomaterials in rodent models of disease in order to predict the risk for human disease.

BACKGROUND

Lung Exposures in Rodents

Inhalation studies are most relevant because they provide information on "real world" exposures and therefore more accurately model the true nature of deposition patterns for particles and fibers. Rodent studies show that inhaled CNTs are deposited in the distal regions of the lung, including alveolar duct bifurcations and alveolar epithelial surfaces [Ma-Hock et al. 2009; Pauluhn 2010; Mitchell et al., 2007; Shvedova et al., 2008; Ryman-Rasmussen et al. 2009 a,b]. CNTs are then mainly taken up by alveolar macrophages, which then remove shorter nanotubes (i.e., <10 μm) through airway mucociliary clearance or through the pleural lymphatic drainage. However, some individual CNTs evade phagocytosis by macrophages uptake and are internalized within epithelial cells or mesenchymal cells, or within the extracellular matrix [Ryman-Rasmussen et al. 2009a].

The site of deposition for CNTs following an inhalation exposure is determined by a variety of factors such as size, shape, electrostatic charge, and aggregation. Changing the surface features of CNTs through functionalization (e.g., carboxylation) can alter aggregation status and influence the toxicological outcome in the lung [Wang et al., ACS Nano 2011; Bonner et al., 2013]. In general, studies with mice show that inhaled, well-dispersed CNTs are deposited throughout lower airways of the lung and alveolar compartments [Figure 1]. The majority of published studies on CNT exposure in rodents employ intratracheal instillation (IT) or oropharyngeal aspiration (OPA) techniques rather than inhalation, due mainly to the relative ease and low cost of performing IT or OPA compared to inhalation. IT or OPA techniques deliver an aqueous bolus of CNT and therefore do not precisely reproduce the deposition patterns achieved by inhalation exposures with dry aerosolized or nebulized suspensions of CNTs. Many of the early reports of granulmona in the lungs of rodents caused by CNTs could be due to poor dispersion and non-specific reactions; i.e., highly agglomerated CNTs attract focal accumulations of mononuclear cells that stimulate the formation of fibrotic scar to "wall off" the CNT agglomerate. However, significant improvements have been made in dispersing CNTs in aqueous suspension by using surfactant-containing media to improve dispersal of CNTs for IT or OPA delivery to the lungs of rats and mice [Mercer et al. 2008].

CNTs are cleared from the lung by macrophage-dependent mechanisms; either via the airway mucociliary apparatus or via the pleural lymphatic drainage [Figure 2]. The mucociliary apparatus is comprised of a coating of mucus on the surface of the airways that is constantly moving up the airways by the coordinated movement of cilia on the airway epithelium [Bonner 2008]. Macrophages with engulfed particles or fibers migrate to the distal portion of small airways where they are transported by the escalator to larger airways and ultimately out of the trachea where they are swallowed or expelled through coughing. Migration of macrophages containing CNTs across the pleura, through stomata in the mesothelium that covers the pleura, could cause adverse effects (e.g. DNA damage to mesothelial cells) as CNTs could possess some physical characteristics (e.g., high aspect ratio, durability) that resemble asbestos fibers [Bonner et al., 2010a; Donaldson 2010]. However, the relative carcinogenicity of CNTs