**Diffuse Fibrotic Response Due to Deposition of Submicron Single Walled Carbon Nanotubes**

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The lungs have been demonstrated to have a rapid and significant fibrotic response to single walled carbon nanotubes (SWCNT) in either their raw or metal catalyst free purified form. This fibrotic response has been characterized as large granulomatous lesions around and within lung deposits of SWCNT. In the typical animal model, the SWCNT deposits that are the focus of the granulomatous responses are sufficiently large that they can be visualized in light microscopic sections (2 to 20 microns diameter). We have recently demonstrated that a generalized thickening of the alveolar walls occurs throughout the lungs and is not limited to tissue directly associated with the large, visible SWCNT deposits. The total collagen produced in this generalized fibrosis of the alveolar wall is significant, being approximately the same as the collagen produced in the large granulomatous lesions. We hypothesized that the more generalized fibrotic response was due to submicron SWCNT distributed widely throughout the lungs. To test this hypothesis, we gold-labeled SWCNT and used the labeled SWCNT in aspiration studies. Silver-enhancement of gold-labeled, purified, SWCNT was used to identify sub-micron SWCNT in light microscopic sections. Pharyngeal aspiration in C57BL/6 mice was used to determine the pulmonary delivery and toxicity of the gold-labeled SWCNT. After aspiration of 40ug/mouse, the mice were sacrificed and the lungs preserved by vascular perfusion of fixative at 1 hour, 1, 3 and 7 days after aspiration of gold-labeled SWCNT. Aspiration of phosphate-buffered saline (PBS) was used as a negative control. Electron microscopy of lung sections demonstrated gold-labeled SWCNT in the interstitium of the alveolar wall 3 days after aspiration. Light microscopy of silver-enhanced sections from mice given gold-labeled SWCNT demonstrated the presence of a significant number of deposits, which were much smaller and more widely distributed throughout the lungs than the larger SWCNT previously identified. In particular, a significant number of deposits were found in the distal alveolar region and the alveolar lining of the pleural surface. Morphometric estimates based on the silver-enhanced sections suggest that the sub-micron SWCNT account for $1/20^{th}$ of the total SWCNT dose in the lungs yet produce approximately the same collagen response in the lungs. These results demonstrate that the fibrosis in the alveolar interstitium is due to the presence of sub-micron SWCNTs and indicate that individual nanotubes and/or nanoropes have substantial fibrotic potential.

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