121. TGF-B1 Mediated SWCNT Induced Lung Fibrosis Depends on the Upstream Osteopontin Stimulation

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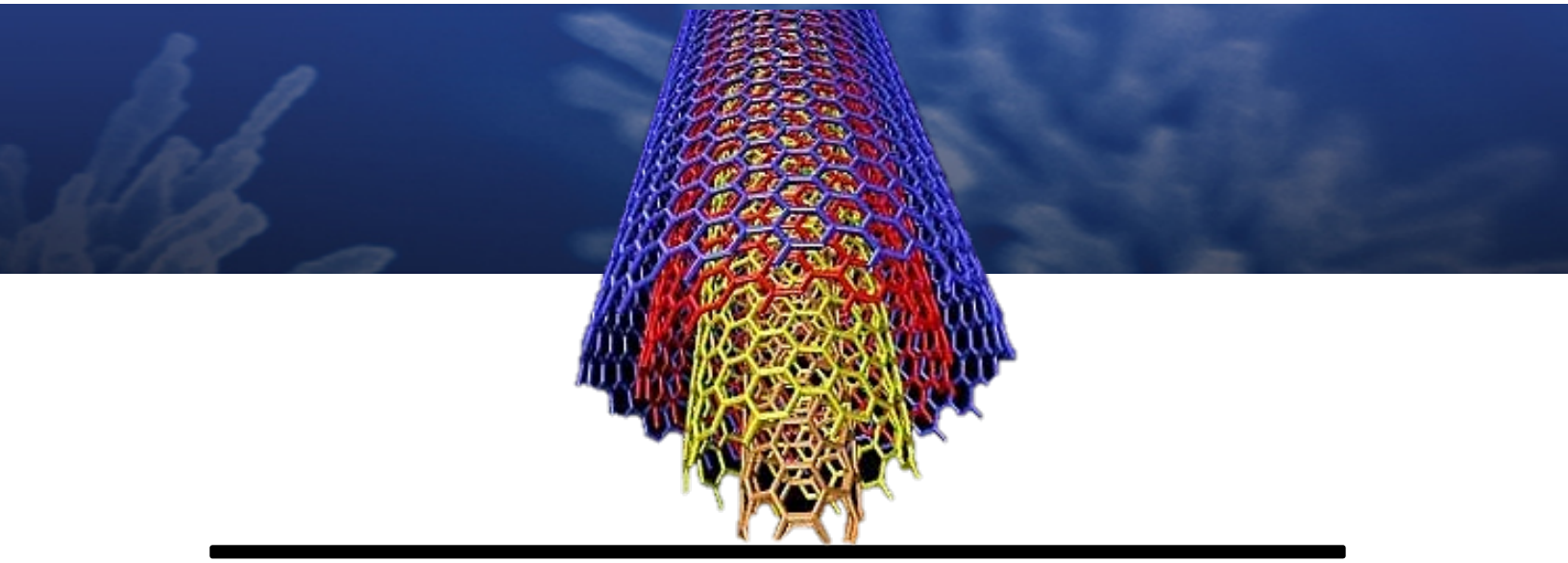
Several studies have demonstrated that single-walled carbon nanotubes (SWCNT) exposure caused pulmonary fibrosis with a rapid inflammatory onset and subsequent granulomas formation through mechanisms involving epithelial-mesenchymal transition, myofibroblast ROS-dependent differentiation /recruitment accompanied by the release and interplay of various cytokines/chemotactic factors. The transforming growth factor-β (TGF-β) has been recognized as a central player in the robust pulmonary inflammatory response involved in the development of granulomas and interstitial fibrosis. However, the role of glycoprotein osteopontin (OPN) in TGF-β1 mediated fibrosis has not been fully explored. We used OPN-knockout (OPN-KO) and wild type (WT) C57BL/6 mice to investigate pulmonary fibrotic response upon exposure to SWCNT (40 μg/mouse). Reduced release of pro-inflammatory cytokines (MCP-1, TNF-α, IL-6), diminished pulmonary damage markers, and less pronounced neutrophil accumulation were found in broncho-alveolar lavage (BAL) of OPN-KO mice as compared to WT mice. Morphological examination revealed markedly decreased formation of granulomatous lesions along with diminished collagen deposition in the lungs of OPN-KO mice. While a significant increase in the level of TGF-β1 was found in BAL of WT mice, TGF-β1 readings in OPN-KO animals remained unaltered. In line with this, significantly reduced levels of TGF-β1 were detected when RAW 264.7 cells and MLE-15 cells exposed to SWCNT (24 hours, 6 μg/cm^2 to 48 μg/cm^2) were pre-treated with an OPN-blocking antibody. To the best of our knowledge, this is the first report to demonstrate that OPN may play a crucial role in TGF-β1 mediated SWCNT induced lung fibrosis. Supported by grants NORA 933051G and FP7-NANOSOLUTIONS no. 309329.

Keywords: Carbon-based nanomaterials, In vitro toxicology, In vivo toxicology, pulmonary fibrosis



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