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**TITLE:** PATHWAY FOCUSED PROTEIN PROFILING INDICATES DIFFERENTIAL FUNCTION FOR IL-1B, -18 AND VEGF DURING INITIATION AND RESOLUTION OF LUNG INFLAMMATION EVOKED BY CARBON NANOPARTICLE EXPOSURE IN MICE

**PUBLISHED:** December-09

**CITE:** Particle and Fibre Toxicology, 2009, 6: 31 (14pp)

**ABSTRACT:** Carbonaceous nanoparticles possess an emerging source of human exposure due to the massive release of combustion products and the ongoing revolution in nanotechnology. Pulmonary inflammation caused by deposited nanoparticles is central for their adverse health effects. Epidemiological studies suggest that individuals with favourable lung physiology are at lower risk for particulate matter associated respiratory diseases probably due to efficient control of inflammation and repair process. Therefore we selected a mouse strain C3H/HeJ (C3) with robust lung physiology and exposed it to moderately toxic carbon nanoparticles (CNP) to study the elicited pulmonary inflammation and its resolution. Methods 5 µg, 20 µg and 50 µg CNP were intratracheally (i.t.) instilled in C3 mice to identify the optimal dose for subsequent time course studies. Pulmonary inflammation was assessed using histology, bronchoalveolar lavage (BAL) analysis and by a panel of 62 protein markers. Results 1 day after instillation of CNP, C3 mice exhibited a typical dose response, with the lowest dose (5 µg) representing the 'no effect level' as reflected by polymorphonuclear leucocyte (PMN), and BAL/lung concentrations of pro-inflammatory proteins. Histological analysis and BAL-protein concentration did not reveal any evidence of tissue injury in 20 µg CNP instilled animals. Accordingly time course assessment of the inflammatory response was performed after 3 and 7 days with this dose (20 µg). Compared to day 1, BAL PMN counts were significantly decreased at day 3 and completely returned to normal by day 7. We have identified protein markers related to the acute response and also to the time dependent response in lung and BAL. After complete resolution of PMN influx on day 7, we detected elevated concentrations of 20 markers that included IL1B, IL18, FGF2, EDN1, and VEGF in lung and/or BAL. Biological pathway analysis revealed these factors to be involved in a closely regulated molecular cascade with IL1B/IL18 as upstream and FGF2/EDN1/VEGF as downstream molecules. Conclusion Considering the role of VEGF, FGF2 and EDN1 in lung development and morphogenesis together with the lack of any evident tissue damage we suggest a protective/homeostatic machinery to be associated in lungs of stable organisms to counter the CNP challenge as a precautionary measure.