

Tungsten-Carbide-Cobalt Nano-Particles Induces ROS Formation and Angiogenesis

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Powder mixtures of tungsten carbide and metallic cobalt (WC-Co) are widely used in various products and are bio-available in factory settings. Occupational exposure to WC-Co leads to higher rates of pulmonary fibrosis and lung cancer, both of which involve angiogenesis. The mechanisms for disease pathogenesis with exposure to WC-Co are unknown. Nano-particles are engineered structures with at least one dimension of 100 nanometers or smaller and questions have arisen regarding the role of nano-particles in health and disease. In this study, we showed WC-Co nano-particles increased HIF-1alpha protein in Beas-2B lung epithelial cells whereas HIF-1beta was unchanged. VEGF mRNA was increased with WC-Co nano-particle treatment. Further, VEGF transcriptional activity, determined by luciferase reporter assay, increased in with WC-Co nano-particle treatment whereas fine particles had no effect. WC-Co nano-particles also induced transcriptional activity of NF-kappaB and AP-1. Lung epithelial cells treated with WC-Co nano-particles, but not fine particles, showed increases in angiogenesis in the chick chorioallantoic membrane (CAM) model. Angiogenesis was prevented with pre-treatment with adenovirus containing the ROS scavenger catalase, suggesting the involvement of ROS in angiogenesis. ROS generation, evaluated by DCFH-DA staining, increased in lung epithelial cells treated with WC-Co nano-particles whereas fine particles did not increase ROS formation. WC-Co nano-particle-induced ROS generation was prevented with pre-treatment with an NADPH Oxidase inhibitor and a Rac1 inhibitor, suggesting Rac1-dependent and NADPH oxidase-induced ROS formation. Further, NADPH oxidase activity, determined by the lucigenin chemiluminescence method, increased in Beas-2B cells in a dose-dependent manner with WC-Co nano-particles, whereas fine particles showed no effect. Pre-treatment of lung epithelial cells with an NADPH oxidase inhibitor and a Rac1 inhibitor prevented the increase in NADPH oxidase activity with WC-Co nano-particle treatment. These results identify multiple signaling molecules that are induced by WC-Co nano-particle treatment, and elucidate the potential molecular mechanism of their regulation in cells. This information may be useful for preventing potential damage from WC-Co exposure in the future and understanding the pathogenesis of nano-particle-induced diseases.