Titanium Dioxide Nanoparticles And Diesel Exhaust Particles Induced Neuro-Inflammatory Modulation In Human Airway Epithelial Cells

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Exposure to nanoparticles during production, distribution and use can cause significant health problems. Nanoparticles initially were considered inert, but recent studies have shown that some types can induce neuro-pulmonary inflammation in animal models. Similarly, diesel exhaust particles (DEP) associated with the combustion of diesel fuel can exacerbate allergic airway responses in mice. Human airways are the primary target of these particles, especially when they are in the form of aerosols. A detailed understanding of the airway neuro-responsiveness to nanoparticles is limited in literature. Therefore, we explored the cytotoxicity and neuroimmuno-modulation of human airway nasal, tracheal, bronchial and alveolar epithelial cells exposed to fine TiO_2 (< 5 µm) , nano TiO_2 (21nm) and DEP 2975 at concentrations ranging from 1-100µg/ml in PBS for 24 hours at 37°C. Cell viability was significantly reduced in a dose-dependent manner after exposure of human airway epithelial cells to TiO_2 particles and DEP. At 10 µg/ml of TiO_2-NP, 70.9% alveolar cells were viable as compared to 80% and 77% cells viable cells when exposed to TiO_2-FP ($p<0.01$) and DEP ($p<0.01$), respectively. The bronchial epithelial cell and alveolar cell patterns of cell death were comparatively similar, whereas response was much different with nasal and tracheal epithelial cells. We also measured the nerve growth factor (NGF), brain derived growth factor (BDNF) and their receptors tyrosine kinase A (trkA), tyrosine kinase B (trkB) and low affinity neurotrophin receptor $p75^{NTR}$. Flow cytometric and real time PCR analysis revealed significant modulations in neurotrophins and their receptors in all the airway epithelial cells studied, but variation was observed with respect to the particle size and cell lines evaluated. NGF and p75 levels were higher following TiO_2-NP exposure in nasal, bronchial and alveolar cells; no such up-regulation was evident in tracheal epithelial cells. Exposure to fine-sized TiO_2 particles resulted in up-regulation of NGF and TrkA in bronchial cells with significant down-regulation of $p75^{NTR}$. Alveolar epithelial cells exposed to 10µg/mL of DEP showed higher levels of NGF, TrkA and $p75^{NTR}$. Multiplex analysis of inflammatory cytokines showed significant up-regulation in several cytokines and chemokines upon exposure to DEP or TiO_2 in all the cell lines studied. In conclusion, the data suggest that TiO_2-induced secretion of NGF could lead to neurogenic-mediated immuno-inflammatory mechanisms that play an important role in airway inflammation and hyperesponsiveness.

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