Fate Of Airway Epithelial Cells Exposed To Titanium Dioxide Nanoparticles: Ngf Regulated Apoptotic Death

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Recent studies revealed that nano-sized TiO_2 can cause inflammatory response in airways of rats and mice, fibrosis or lung tumors in rats and DNA damage in Chinese hamster ovary (CHO) cells, Syrian hamster embryo fibroblasts and human lymphoblastoid cells. The primary human airway bronchial epithelial cells exposed to nanoparticles elicit high levels of neurotrophins, which has a significant role in modulating the cell cycle, cell proliferations and inflammatory responses. Nerve Growth Factor (NGF) can bind to tyrosine kinase A (trkA) and with $p75^{NTR}$ depending the physiological state of the cell. It has also been reported that unprocessed NGF precursor, proNGF, binds p75NTR preferentially over trkA, and this selective binding of proNGF to $p75^{NTR}$ leads to apoptotic death of cells. The cytotoxicity observed on TiO_2 treatment was differed with cell type of the airway niche and particle size. Here we try to explore the possible molecular mechanism that leads to the toxicity of TiO_2 and the downstream targets of NGF pathway. TiO_2 mediated induction of NGF, was dependent on cell type, particle size and dose. To evaluate the mechanism of TiO_2 mediated toxicity, the bronchial epithelial cells were exposed to TiO_2 (10µg/mL) and the apoptosis and necrosis were measured. Annexin-V and propidium iodide (PI) staining demonstrated that TiO_2-NP induced cell death through apoptosis was highest in bronchial cells (22.0±2.6%) compared to nasal epithelial cells (14.0±0.5%; $p<0.001$). However, nasal epithelial cells following TiO_2 fine particle exposure were more diverted to necrotic death (7.4±1.4% in bronchial vs. 18.6±1.0% in nasal; ($p<0.0004$). We observed significant up-regulation of $p75^{NTR}$ (protein and mRNA) along with lowered co-expression of trkA in bronchial epithelial cells. To further understand the NGF mediated apoptotic pathway, we blocked the low affinity receptor $p75^{NTR}$ expression using $p75^{NTR}$specific antibody resulted significant reduction in apoptosis induced by TiO_2. We also measured the $p75^{NTR}$ downstream stress kinase p-JNK during mitochondrial induced apoptotic cell death. Immunoprecipitation experiments further confirmed significant binding of NGF to $p75^{NTR}$ receptor protein. In conclusion, our study clearly elucidates that the TiO_2 mediated differential expression of neurotrophins along the respiratory tract modulates cellular responses that lead to apoptosis and is modulated by NGF.

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