Nano-Titanium Dioxide Mediated-Autophagy in Human Mesenchymal Stem Cells

Yongli Shi, Feng Wang, Santosh Yadav and He Wang

Department of Environmental Health Science and Cancer Center & Louisiana Cancer Research Consortium, Tulane University, New Orleans, LA.

Abstract

Introduction: Titanium Dioxide Nanoparticles (TNP) are increasingly used and there is a potential for human exposure. The biological effects of TNP are not fully known. Assessment of TNP-related health risk is needed to protect the wellbeing of community. TNP can be absorbed into blood stream and distributed to bone marrow where mesenchymal stem cells (MSC) reside. Moreover, TNP can accumulate in the bone marrow and exert long term effects on these cells. Because MSC are important multi-potent cells, harmful effects of TNP on them may lead to serious consequences.

Specific Aims: This study is designed to investigate the cell death process of MSC in response to TNP exposure and the underlying mechanisms. Programmed Cell Death (PCD) includes type I and II pathways, apoptosis and autophagy, are investigated to reveal which type of PCD MSC will take in response to TNP. This clarification will lead to better understanding of biological effects of TNP.

Research Methodology: The apoptosis (PCD I) induced by TNP in human bone marrow derived MSC was determined by cleavage of caspase-3 and PARP using western blot method. The autophagy (PCD II) induced by TNP in MSC was determined by formation of autophagosomes, induction of LC3-II, reversion of LC3-II from LC3-I, using AO staining and western blot methods. The pathways of autophagy were also studied by utilizing inhibitors of ROS and MAPK pathway.

Results: Our results showed that: 1) TNP induced autophagic rather than apoptotic response in human bone marrow derived MSC; 2) NAC, a ROS inhibitor, could inhibit induction of LC3II, a marker of autophagy. Concurrently, it inhibited activation of ERK1/2, p38 and JNK. SB203580 and SP600125, inhibitors for p38 and JNK, leaded to inhibition of autophagy induction. However, both U0126 and PD98059, inhibitors of ERK1/2, failed to affect the induction of autophagy.

Conclusion: Our data provide the first evidence that TNP induces autophagy through production of ROS rather than interference with ROS-induced MAPK signaling pathways in human bone marrow derived MSC. Given the growing use of TNP, these findings raise concern about potential health hazards associated with TNP exposure.