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Toxicity of metal oxides NP on rat macrophages: A combined transcriptomic and proteomic study

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The paucity of biomarkers to predict the toxicity of nanoparticles (NP) makes important to identify key pathways linked to a toxic exposure of lung to NP. In this study, we focused on the impacts of three metallic NP on NR8383 alveolar macrophages to evaluate modifications in transcriptome and proteome profiles after exposure to sub-toxic doses of zinc oxide (ZnO), zinc ferrite oxide ($ZnFe_2O_4$), and iron oxide (Fe_2O_3) NP. The cytotoxic potency of NP was evaluated by extracellular LDH measurement and by WST1 assay. A significant induction of membrane damage and reduction of NR8383 viability were noticed after 24 hours exposure to the ZnO and $ZnFe_2O_4$ NP. To understand the interactions that occur and the biological consequences of exposure of lung to NP, optimal conditions where NR8383 cells remained viable during the sub-toxic doses exposure. Then, gene expression and protein production were investigated by microarray profiles and mass spectrometry methods, respectively. Genomic study showed 1036, 1274 and 3763 differentially expressed genes following 4 hours exposure to sub-toxic doses of ZnO, $ZnFe_2O_4$ and Fe_2O_3 NP, respectively. Proteomic study revealed 348, 784 and 872 differentially produced proteins after 24 hours, respectively. The main involved pathways in genomic study were eIF2, eIF4/p70S6K and protein ubiquitination signalings. Mitochondrial dysfunction, oxidative phosphorylation, sirtuin signaling, protein ubiquitination, unfolded protein response and cholesterol biosynthesis were the main pathways affected revealed by the proteomic study after exposure to the 3 NP. The use of transcriptomic and proteomic platforms, with appropriately designed experimental conditions, enabled the observation of the early biological impairment induced by ZnO, $ZnFe_2O_4$ and Fe_2O_3 NP. The data allowed us to suggest that the protein synthesis default was the effect biomarker for the three NP studied and the metallothioneins gene overexpression was the exposure biomarker for zinc element.

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