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Genotoxicity of Nanoparticles

Oleksandr H Minchenko[1], Olha v rudnytska, Dariia O Tsymbal[1], Olha V Rudnytska[1], Dmytro O Minchenko[1,2]

[1]Palladin Institute of Biochemistry, National Academy of Sciences of Ukraine, Ukraine
[2]Bohomolets National Medical University, Ukraine

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Abstract:

Various nanoparticles have distinctive and remarkable material properties, different from bulk materials with all the same chemical composition, and potential technology applications, including those in biology and medicine. Many of them have recently emerged as a new option for cancer treatment, bioengineering, and gene therapy, but inconsistent data on cytotoxicity and limited control over all such nanoparticles behavior currently in restrict predictability of such applications. We have studied genotoxicity of different nanoparticles: single-walled carbon nanotubes (SWCNT), C60 fullerene, cerium dioxide, chromium disilicide, and titanium nitrite nanoparticles [1 - 7].

Most nanotubes, including single-walled carbon nanotubes (SWCNT), have a highly hydrophobic surface and a non-biodegradable nature that contributes to their reduced biocompatibility, limiting their biomedical applications, with all the growing concerns about their chronic toxicity. It is important to note that different variants of carbon nanotubes exhibit diverse toxicity both in vitro and in vivo. The toxicity of carbon nanotubes is attributed to their physicochemical properties, including structure and dose offered to cells or organisms and can elicit toxicity through numerous mechanisms. Similar results were shown for titanium dioxide [8]. Treatment of three different cell types by variable titanium dioxide nanoparticles (nanoneedles, titanate scrolled nanosheets, and gel-sol- based isotropic nanoparticles) leads to significant perturbation of cellular homeostasis disturbing cell proliferation, cellular ion content, as well as diverse stress pathways) [8]. It is interesting to note that these variants of titanium dioxide nanoparticles were internalized at various degrees and their toxicity depended on both titanium content and shape of nanoparticles, which impacted on intracellular homeostasis thereby leading to endoplasmic reticulum stress.

We have shown that different nanoparticles such as SWCNT, C60 fullerene, cerium dioxide, titanium nitrite, and chromium disilicide nanoparticles strongly disturb genome stability leading to functional reprogramming genome through development of the endoplasmic reticulum stress, which can be an earlier biomarker for nanotoxicological evaluation according to Chen et al. [9]. All these nanoparticles affect the expression of numerous genes; preferentially stress responsible genes, including oncogenes, which are associated with cell proliferation, migration, cancer development, and invasion. Thus, in normal human astrocytes and glioma cells the SWCNT (2, 10 and 50 ng/ml of medium for 24 hrs) affects the expression of a number of genes encoding proteins associated with immune response, cell cycle control, cell proliferation, and apoptosis as well as genome stability. We observed a dose-dependent and strong down-regulation effect of SWCNT on the expression level of a cell surface glycoprotein HLA-DRA (major histocompatibility complex, class II, DR alpha) and CCND2 (cyclin D2). The effect of these carbon nanotubes on the expression level of PARVB (parvin beta), PHLDA2 (pleckstrin homology-like domain, family A, member 2) PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3), and PFKFB4 was also suppressive but less prominent. At the same time, the expression of HLA-F (major histocompatibility complex, class I, F), DUSP1 (dual specificity phosphatase 1), DTNA (dystrobrevin alpha), LMNB1 (lamin B1), and HTRA1 (high temperature requirement A1) genes was up-regulated in glial cells treated with different concentrations of single-walled carbon nanotubes [1, 2]. It is interesting to note that single-walled carbon nanotubes affect the alternative slicing pre-mRNA DTNA, PFKFB3, and PFKFB4 changing the functional activity of proteins at post transcriptional level.

Obtained data show that single-walled carbon nanotubes may affect an immune response, in articular through suppression of HLA-DRA gene expression as well as via up-regulation of the expression level of HLA-F, because leukocyte antigen HLA-F is a non-classical HLA-class I molecule which has attracted attention as an important immunosuppressive molecule. Its expression was found to be enhanced in gastric adenocarcinoma, breast cancer, esophageal squamous cell carcinoma, hepatocellular carcinoma, and neuroblastoma and correlated with tumor cell invasion and metastasis. These carbon nanotubes significantly disturb cell-cycle regulation through strong suppression of CCND2, which is a regulatory component of the cyclin D2-CDK4 complex that phosphorylates and all the inhibits members of the retinoblastoma in protein family including RB1 and regulates the during G(1)/S transition. Furthermore, deregulation of nuclear lamina protein LMNB1 (lamin B1) expression in human astrocytes following treatment with single-walled carbon nanotubes indicates the possibility that these nanomaterials can also affect genome stability. This nuclear protein participates in a senescence program, which often induced by genotoxic stress and is important for malignant tumor suppression. It is interesting to note that the nuclear protein lamin B1 fragment can non-covalently attach to single-walled carbon nanotubes and deliver these nanoparticles to the nucleus due to its exposed nuclear localization sequence.

Furthermore, a dose-dependent up-regulation of serine protease with IGF-binding domain PRSS11 (HTRA1), a stress responsive polyfunctional enzyme, which regulates the availability of insulin-like growth factors by cleaving IGF-binding proteins, in normal human astrocytes treated by SWCNT also reflects genotoxicity of nanotubes. Increased expression of PHLDA2 gene, which is associated with glioblastoma and other types of cancers, in treated by carbon nanotubes glial cells can also contribute to possibility of tumor development because this protein inhibits cell proliferation, migration and invasion, as well as induces apoptosis. It is possible that changes in the expression of PARVB gene induced by SWCNT have similar significance because this adapter protein functions in tumor suppression and plays an important role in integrin signaling, involved in the reorganization of the actin cytoskeleton as well as in cell adhesion, cell spreading, establishment or maintenance of cell polarity, and cell migration.

Similar results were obtained with many other nanoparticles (C60 fullerene, cerium dioxide, chromium disilicide, and titanium nitrite) both in vitro and in vivo. Thus, exposure of human glial cells with cerium dioxide nanoparticles (0.17 and 0.34 mg/mL of medium) during 20 h significantly decreases the expression level of transcription factors TBX3, E2F8 and FOXF1 mRNAs, being stronger for higher doses of nanoparticles as well as IGFBP1, IGFBP2, and LIF, which are important

for control of cell proliferation and survival. C60 fullerene affects the expression level of LIF1, CCNG1, SLC1A1, PRKCA, TBX3, IGFBP1, IGFBP2, FOXF1 and TSPAN13 genes in time dependent manner as well as activates glial cell proliferation via down-regulation of some tumor suppressors. Strong genotoxic effect was shown for chromium disilicide and titanium nitride nanoparticles in vivo. We studied the expression level of genes encoding important regulatory factors such as IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, SNARK/NUAK2, CD36, FABP4, PECAM1/CD31, NAMPT, UPS7, E2F8, FAS/TNFSF6, TBX3, and IL13RA2) in the liver of treated by these nanoparticles mice [3, 4, 7]. Both chromium disilicide and titanium nitride affect the expression most of these genes in mouse liver preferentially in the same way but effect of chromium disilicide usually was much stronger. All studied genes are endoplasmic reticulum stress responsible and different nanoparticles affect the expression of these genes preferentially activate genes encoding proteins with prooncogenic and cell surviving properties and strongly deregulate very important tumor suppressor genes as well as many other regulatory factors and enzymes.

Therefore, present study demonstrates that different nanoparticles (single-walled carbon nanotubes, C60 fullerene, cerium dioxide, chromium disilicide, and titanium nitrite nanoparticles) had many variable effects on the expression of many studied genes in a gene specific manner, which possibly reflect a strong genotoxic activities of studied nanoparticles and their effect on important regulatory mechanisms controlling cell proliferation and cell survival, cell cycle and apoptosis as well as immune response and genome stability. Moreover, our results suggest more cautions needed in biomedical applications of different nanoparticles. However, the detailed molecular mechanisms of observed changes in the expression of studied genes warrant further investigation.

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