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Nanoparticle Technology as a Double-Edged Sword: Cytotoxic, Genotoxic and Epigenetic Effects on Living Cells

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ABSTRACT

Nanoparticles are considered as powerful tools in nanotechnological applications. Due to their unique physicochemical properties, their interactions with different biological systems have been shown. Nanomaterials have been successfully used as coating materials or treatment and diagnosis tools. Nevertheless, toxic effects of nanoparticles *in vitro* and *in vivo* have also been reported. Here, we summarize the current state of knowledge on exposure routes, cellular uptake and toxicological activities of the commonly used nanoparticles. In this context, we discuss the mechanisms of toxicity of nanoparticles involving perturbation of redox milieu homeostasis and cellular signaling pathways.

Keywords: Nanoparticles; Nanotoxicology; Genotoxicity; Cytotoxicity; Epigenetics

1. Introduction

It is widely accepted that nanoparticles (NPs) and nanomaterials could be successfully used in food technology, cosmetics, modern chemistry and biomedicine. The attributes of organic and inorganic nanoparticles, such as small size, composition, surface structure, solubility, shape and aggregation allow for unlimited modifications of their basic properties such as diffusivity, targeting, stability, solubility, half-life in circulatory system and controlled drug release. Due to such unique features, nanoparticles have the advantage over traditional therapeutic and diagnostic agents [1-4]. Nanoresearch is focused on many life-sciences including applications in environmental, health and safety sciences.

Nevertheless, very little is known how NPs affect humans and the environment. Here, we resume current information on negative effects of NPs especially including their toxicity (**Figure 1**) [5-13].

2. Exposure Routes, Cellular Uptake and Toxicological Effects

The organism has several semi-open interfaces for exchange some substances with the environment. The same interfaces are the primary routes of exposure of nanoparticles such as inhalation, dermal absorption and ingestion.

Routes of NPs exposure is highly affected by a plethora of factors e.g. NPs stability *in vivo* and their toxicokinetics, absorption, distribution, conversion to more toxic metabolites, interaction with macromolecules [14].

The different compartments of the human respiratory track act as a nanoparticle filter. If a nanoparticle is very small (<2.5 μm), it is very likely that it would reach the alveolar region. After absorption, nanoparticles can enter bone marrow, spleen or heart cells (through blood or lymph). Nanoparticles could associate, coagulate and in turn cause a disturbance of cardiac rhythm or nerve endings in the airway epithelia and the central nervous system [15]. Skin is the largest organ of the integumentary system consists of multiple layers of ectodermal tissue. Damaged skin is an ineffective particle barrier and even very small wound may accelerate nanoparticle uptake [16]. Chemical penetration into skin can occur through pilosebaceous or swat gland pores. Nanoparticle parameters important for overcoming the cell membrane barrier are: size, charge, shape, nanoparticle coating, hydrodynamic diameter, isoelectric point, pH gradient. For example, TiO_2, ZnO (30 - 200 nm) and nail-shaped NPs (39 - 45 nm) can penetrate only the outer layer of the epidermis, while spherical Quantum dots (QDs) (15 - 45 nm) are able to reach epidermis and even dermis [17]. In clinical studies, silver nanoparticles are used in coated dressings which are exerted in burnings treatment. Be-

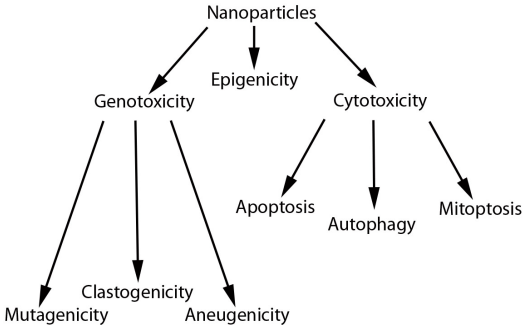

Figure 1. Potential toxic effects of nanoparticles on living cells.

sides good control of wound infection, they trigger abnormal elevations of blood silver levels and argyria as well. Nanoparticles can be also ingested directly in food, water and drugs. Nanocopper substances are several folds more toxic than copper. Nanocopper can also cause liver and kidney damage. After ingestion nanocopper particles react with hydrogen ions (gastric juice) and lead to a massive formation of bicarbonate ion. Alkalosis caused by overload of bicarbonate ions triggers hypopnea symptom and electrolyte disturbance [18]. Nanoparticles can enter the cell via diverse mechanisms such as simple diffusion across the cellular membrane, endocytosis, and phagocytosis or through ion canals or pores [19]. The key mechanisms of nanoparticle uptake include clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis or phagocytosis. Clathrin-mediated endocytosis is involved in non-macrophage cell nanoparticle (50 - 200 nm) uptake and it leads to accumulation of extracellular macromolecules into clathrin-coated vesicles fused to early endosomal vesicles [20]. With endocytosis, particles are taken up via small pits in the membrane which is mediated by special receptors [21]. Macropinocytosis occurs from ruffled regions of the membrane within vacuoles (~0.5 - 5.0 μm) [22]. During phagocytosis, cell binds and internalizes particles bigger than 0.75 μm, and microglia are specialized in such uptake [23]. The same nanoparticle can be captured via various mechanisms. For example, diamond powder particle uptake is based on macropinocytosis or on clathrin-mediated endocytosis pathways and uptake type affects intracellular metabolism [5]. Additionally, physicochemical parameters (coating, charge) of QDs may discriminate NPs uptake type [24]. After entering the cell, the same nanoparticle can cause different toxic effect which depends on cell type affected (**Table 1**). Several factors have been found to modulate NPs toxicity such as individual NPs physicochemical properties: size, charge, concentration, outer coating bioactivity (capping material, functional groups), and oxidative, photolytic, and mechanical stability [25,26].

NPs can affect cytophysiology of the cell at different levels such as cellular, organelle level as well as at the level of genetic information which in turn may contribute to cytotoxicity, cancer development and aging [15,27]. NPs are so small that they can penetrate the small capillaries throughout the body and pass through biological membranes [28]. NPs (<100 nm) can enter the cell, NPs (<40 nm) can enter nucleus, and NPs (<35 nm) can pass the blood brain barrier. Moreover, it has been reported that metallic, metal oxide, semiconductor nanoparticles, polymeric nanoparticles and carbon based nanoparticles may cause cytotoxic effects, which is dose-, cell type- and treatment time-dependent [15,29]. NPs such as silver NPs (15 nm), molybdenum NPs (30 nm) and aluminum NPs (30 nm) were found to cause diverse effects on mouse type A spermatogonia. Molybdenum NPs at range of concentrations studied did not affect the cells, whilst silver NPs at concentration under 10 μg/mL induced dramatic changes such as cell clumping, precipitation, shrinkage and apoptosis. Aluminum nanoparticles did not cause any damage at concentrations below 10 μg/mL (formed aggregates, their effect on mitochondrial function could not be checked). Mitochondrial function and cell viability were reduced by silver NPs at the lowest concentration used and by molybdenum NPs at concentration of 50 μg/mL. Silver NPs increased membrane leakage, whilst molybdenum NPs affected the membrane integrity at lower concentrations [30]. Additionally, cytotoxicity of gold NPs was reported to be associated with their size and not with ligand construction. Particles in the 1 - 2 nm size range are highly toxic, whereas smaller and bigger than that are not toxic and different cell death pathways (necrosis or apoptosis) are involved with different uptake kinetics or different targeting [31]. 24-h exposure to ZnO and TiO_2 had a tremendous toxic impact on human skin fibroblast cells, while 4-h exposure caused only a mild adverse effect [29]. Besides cytoxicity, genotoxicity is another important factor in nanoparticle toxicity studies, especially for metal NPs, quantum dots and fullerenes (**Table 1**). Chromosomal fragmentation, point mutations, alterations in gene expression profiles, DNA strand breakages were also observed [15]. One of the assays used to assess the genotoxic potential of nanoparticles is the Ames Test. It was shown that TiO_2 NPs and C-60 are able to induce deletion mutations in gptΔ transgenic mutation assay system. TiO_2 (5 nm) caused a 2.2-fold increase in mutation yield in mouse embryonic fibroblast cells (MEF). At higher concentrations, TiO_2 did not induce further increase in mutation yield. However, C-60 treatment stimulated dose-dependent induction of mutation in MEF cells [32]. Also, NPs can induce large chromosomal rearrangements such as aneuploidy [33].

As it has been already noticed, nanoparticle localization within the cell and interaction type with cellular

Table 1. Selective toxicity of NPs.

Selected nanoparticles	Cells	Physiological effect	Ref.
Zinc oxide nanoparticles (ZnO)	Hepatocytes	Oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis	[73]
	Renal cells	Nephrotoxicity and kidney metabolism alterations	[8]
	Neurons	Damage of the ionic homeostasis and the physiological functions of neurons	[74]
	Fetal lung fibroblasts	Cellular mitochondrial dysfunction, morphological modifications and apoptosis	[75]
	Lymphocytes	Cytotoxicity and Cytokine Induction	[76]
	Nasal mucosa cells	Cytotoxic, genotoxic and pro-inflammatory effects	[77]
Carbon black nanoparticles (CB-NPs)	Hepatocytes	Inflammatory and genotoxic effects	[56]
	Renal cells	Cytotoxicity	[78]
	Neurons	Neurotoxic effect by disturbing the electrical activity of neuronal networks	[7]
	Lung epithelial cells	Cytotoxicity	[79]
	Lymphocytes	Induction of chromosomal aberrations	[80]
Silica nanoparticles (SiO_2)	Hepatocytes	Hepatotoxicity	[81]
	Neurons	Dopaminergic neurons damage pathways	[82]
	Lung epithelial cells	Toxicity and inflammatory response.	[83]
	Lymphocytes	Cytotoxicity and genotoxicity	[84]
	Fibroblast	Cytotoxicity	[25]
Titanium dioxide nanoparticles (TiO_2)	Hepatocytes	Genotoxicity, carcinogenicity, hepatotoxicity and inflammation	[48,85]
	Renal cells	Induction of oxidative stress and cytotoxicity	[86]
	Neurons	Neurotoxicity	[7]
	Lung epithelial cells	Genotoxicity, mutagenicity and carcinogenicity	[87,88]
	Lymphocytes	Induction of oxidative stress and reduction of immune capacity, Genotoxicity	[27,80]
	Bone-marrow cells	Genotoxicity, induction of oxidative stress, cytotoxicity	[89]
Gold nanoparticles (AuNPs)	Hepatocytes	Atrophy and necrosis	[90]
	Myocardium cells	Cytotoxicity	[91]
	Renal cells	Cytotoxicity	[92]
	Lung fibroblast	Genotoxicity, autophagy	[12,93]
	Bone-marrow cells	Cytotoxicity	[94]
Quantum dots (QDs)	Lymphocytes	Induction of DNA damage, formation of micronuclei (MNs), and generation of DNA adduct (8-hydroxy-2-deoxyguanosine, 8-OHdG)	[95]
Fullerene C-60	Fibroblast	Lipid peroxidation and cytotoxicity	[40]
	Lymphocytes	Genotoxicity	[96]
Silver nanoparticles (AgNPs)	Lung fibroblasts	Cytotoxicity, increased production of ROS, DNA damage, cell cycle arrest	[100]
	Hepatocytes	Cytotoxicity, induction of oxidative stress, decreased the activities of superoxide dismutase and glutathione peroxides, DNA damage	[106]
	Osteoblast	Cytotoxicity, ROS generation, release of lactate dehydrogenase, apoptosis	[107]
	Bone-marrow cells	Cytotoxicity, genotoxicity, mutagenicity, carcinogenicity	[108]
Super-paragnetic iron oxide nanoparticle (SPION)	Renal cells	Genotoxicity, cytotoxicity, changed ROS properties	[109]
	Fibroblasts	Cytotoxicity, loss of adhesion skills, affected signaling transduction pathway	[49,110]

components leading to cytotoxicity or genotoxicity depends on its size. Large particles can induce permanent damage to cell membrane via binding with cellular membrane proteins, whilst small particles can pass through membrane and harm organelles [34] and then, bigger ones can occur in the cytoplasm (mainly in vacuoles) and smaller ones in mitochondria. The interaction between QDs and human peripheral blood mononuclear cells are based on adsorption between amine groups within cell membrane and carboxyl group of QDs, and in some permeabilized cells, QDs distribution was observed only in the cytoplasm and in some other QDs were found even inside the nucleus and in the nucleolus. QDs which could not enter nuclear membrane is localized only inside cytosol membrane [35]. The same nanoparticles such as silica nanoparticles (SiO_2) with diverse type of energy transfer cassettes can localize in different organelles [36]. The interactions between specific nanoparticles and organelles and the effect triggered by such interactions are presented in **Table 2**.

A relation between pH of cell being affected and nanoparticle type entering the cell has also been examined. Nanoparticles were not able to enter the cell in the media at pH 7.4, whilst at pH between 6.3 and 5.4 were found be enabled in different cellular pH compartments, such as lysosomes or early endosomes [37] which could be used in drug delivery applications.

3. Interactions between Nanoparticles and Organic Macromolecules

Toxicological effects of nanoparticles on the cell structure are caused by their indirect or direct interactions with cellular organic molecules [5,38]. The major mechanism underlining NPs-mediated macromolecule toxicity is the disruption of intracellular redox homeostasis which in turn leads to oxidative damage of macromolecules such as lipids, proteins and nucleic acids [38-40]. It is

Table 2. The interactions between specific nanoparticles and organelles and the effect triggered by those interactions.

Organelle	Selected nanoparticle	Physiological effect	Ref
Cellular membrane	AuNPs	-Disappearance of membrane ruffling	[97,98]
	Polylactide (PLA) coated particles	-Increased permeability	[99]
	TiO_2		
Mitochondria	PLA coated particles	-Swollen mitochondria	[97]
	SiO_2	-Mitoptosis	[36]
	AgNPs	-Disruption of the mitochondrial respiratory chain leading to interruption of ATP synthesis	[100]
	CoCr	-Partial fragmentation with limited damage to actin	[101]
Nucleus	Targeted charge-reversal nanoparticles (TCRNs)	-Selective migration into the nucleus	[102]
	AuNPs	-Binding with specific proteins or DNA in a nucleus	[98]
		-Reorganization of nuclear content	[103]
	AgNPs	-DNA damage and chromosomal aberrations	[100]
Nucleolus	Cadmium telluride (CdTe) nanoparticles	-Interactions with chromatin	[66]
	QDs		
Lysosomes	SiO_2	-Cytotoxicity	[36]
Peroxisomes	Fullerene C_{60}	-Changes in acyl-CoA pathways	[104]
Endoplasmic reticulum	PLA coated particles	-Widened ER	[97]
	poly(lactic-co-glycolic acid) PLGA nanoparticles	-Prolonged cross-presentation of the antigen by the antigen-presenting cells leading to enhanced activation of cytotoxic T lymphocytes directed against the tumor cells	[105]
	SiO_2	-Cytotoxicity	[36]
Cytoskeleton	AuNPs	-Depolymerisation of α-tubulin (major component of microtubules)	[101]
	AgNPs		

widely accepted that reactive oxygen species (ROS) play a crucial role in cell metabolism, signaling and homeostasis [41]. Exposure to NPs disturbs the balance between cellular ROS production and detoxification [42]. Moreover, nanoparticle-mediated oxidative stress strictly depends on nanoparticle size, e.g. Mn (40 nm) and Ag (15 nm) treatment caused a 10- and 3-fold increase in intracellular ROS production compared to control conditions, respectively [43]. Similar results were obtained after ZnO [44] and TiO_2 [39] exposure to human myeloblastic leukemia cells and bronchial epithelial cells. It was also shown that C-60-induced lipid peroxidation could be prevented by an addition of antioxidant L-ascorbic acid [40]. Peroxidation of lipids can alter the physicochemical properties of membrane lipid bilayers, especially phospholipids, resulting in loss of membrane flexibility, increased ions permeability and cell death [45]. Interactions of NPs with cellular proteins can also lead to abnormal cytophysiology of the cell [46].

Except nanoparticle-mediated changes in protein folding, NPs can trigger different effects on physiological proteins involved in signal transduction and posttranslational modifications [27,47,48]. It was observed that super-paramagnetic iron oxide nanoparticles could affect signaling transduction pathways, through an increase in expression of genes responsible for production of tyrosine kinases and several members of the kinase C family [49]. NPs could also modulate glycation process, e.g. gold-associated inhibition of collagen glycation [46,50] and silver NPs-mediated inhibition of advanced glycation end-products-induced retinal vascular permeability by targeting the Src kinase pathway was reported [51]. Additionally, the effects of NPs on key genes expression were recorded. After silica nanoparticles (20 nm) treatment, an increase in p53 level and a decrease in Bcl-2 level in hepatoma cells was reported while in hepatic cells cytotoxic effect of SiO_2 was slightly observed [52]. Magnetic nanoparticles of FeO were found to increase the level of Bcl-2 and at the same time decrease the expression of survivin protein which suggested that FeO can enhance the activity of some drugs such as artesunate used for malaria treatment [53]. Nanoparticle genotoxicity can be also mediated through their interactions with nucleic acids. Nanoparticles can cause DNA damage directly or induce a cascade of evens resulting in DNA damage by acting on the membrane [19]. ZnO nanoparticles were found to induce oxidative stress by glutathione depletion with a concomitant increase in hydroperoxide ions, malondialdehyde levels, reactive oxygen species, and lactate dehydrogenase activity and in turn leading to genotoxicity such as DNA fragmentation [54]. Genotoxic properties of SiO_2 and carbon black nanoparticles were also observed after their treatment with human intestinal cell line [55,56]. Oxidative stress-mediated depletion in ATP levels may contribute to limited efficiency of repair processes in the nucleus [57]. Treatment with TiO_2 resulted in an increase in mouse eyespots number (27%), suggesting that TiO_2 increased DNA deletions [10]. Moreover, TiO_2 nanoparticles can induce DNA single-strand breaks, double-strand breaks, oxidative DNA or chromosomal damage in bone marrow cells and maternal exposure to TiO_2 NPs during pregnancy results in DNA deletions in offspring [10]. It was also suggested, that gold nanoparticles implemented to the nuclei of cancer cells caused DNA double-strand breaks and induced cytokinesis arrest in cells which in turn resulted in abnormal cell division and cell death [58]. Fe_3O_4 was found to cause cell cycle arrest in G2/M phase of rat pheochromocytoma cells [59].

4. Epigenetic Toxicity of NPs

As has already been mentioned, some of NPs can penetrate into the nucleus modulating cellular functions and how cell physiology is changed depends on kind of chromatin being affected. NPs-mediated heterochromatin changes cause a dramatic nucleus shrinkage, whilst euchromatin region is only slightly modified. Perturbations in heterochromatin structure may contribute to improper nucleus architecture and its stability. AuNPs were found to modulate heterochromatin connections with lamin proteins and core histones which suggest that NPs could be considered as epigenetic agents [60]. NPs can affect global DNA methylation pattern and/or alter posttranslational modifications of histone proteins. It is known that nanoparticles can induce an increase in ROS production and oxidative DNA damage may affect the ability of methyltransferases to interact with DNA leading to DNA hypomethylation [61]. Moreover, ROS can alter the expression of methylation DNA-regulated genes [62]. On the other hand, it is known that some metal ions, e.g. cadmium ions, can modulate DNA metylotransferase activity [63] suggesting that cadmium can alter DNA methylation pattern. Such an effect strictly depends on duration of cadmium treatment and Cd NPs can be considered as inhibitors or activators of DNA methyltransferase activity. Sites of DNA methylation are controlled by different proteins like MBD (methyl-CpG-binding domain protein) which provide proper enzymatic machinery chromatin silencing [64]. It was observed that with increasing silica nanoparticle doses, the global level of mRNA expression of MBDs gradually decreased. The level of DNA MTase in normal human keratinocytes has changed in the same way which resulted in a decrease of genomic DNA methylation status [65]. CdTe (cadmium telluride) QDs can bind to core histones and the positively charged histones can change the charge and the size of negatively charged QDs which in turn cause an increase in nanoparticle size from 4 to 150 nm and in the

NPs charge from −28.9 mV to +15 mV and stimulate aggregate formation [66]. Furthermore, cadmium telluride QDs in low concentrations are considered as epigenetic activators of oncogene expression. In QDs-treated human breast cancer cells, two epigenetic changes have been observed: histone 3 hypoacetylation and chromatin decondensation leading to reduction in global gene transcription especially for anti-apoptotic genes. Moreover, an increase in p53 protein level by its activation via phosphorylation, nucleus and mitochondria translocation and in turn cell death was recorded in QDs-treated cells [67]. All together, it suggests that histone deacetylases (HDAC) could be potentially used as anticancer therapeutics. Cholesterylbutyrate solid lipid nanoparticles releasing butyric acid have been already shown to act as histone deacetylase inhibitors (HDACIs) [68]. Also, K-182 HDACI-coated cationic nanoparticles resulted in an increase in gene expression and core histone hyperacetylation [69]. AuNPs were found to decrease histone deacetylase activity by binding to sulfhydryl groups on the surface of histone deacetylase 8 [70]. Additionally, nitric oxide (NO) has been found as an important regulator of epigenetic changes. NO induces S-nitrosylation of histone deacetylase 2, which leads to chromatin remodeling and significant inhibition of histone deacetylase activity [71]. Nitric oxide-releasing silica NPs have been successfully used for skin and soft tissue infection treatment [72] which suggests that in future, NO-releasing NPs might be commonly used as histone deacetylase inhibitors for epigenetic treatment of cancer.

5. Conclusion and Future Remarks

Nanoparticles are ubiquitous in the environment and are widely used in medical science (bioimaging, diagnosis and drug therapy delivery). Moreover, their effectiveness in cancer treatment was repeatedly reported. Due to unique physicochemical properties, they are able to cross many barriers, which is not possible for traditional drugs. Nevertheless, exposure to NPs and their following interactions with organelles and macromolecules can result in negative effects on cells, especially they can induce cytotoxicity and cell death. NPs toxicity can be considered useful for cancer therapy, but simultaneously it seems harmful for non-cancer cells. Recent studies also show that nanoparticles can cause epigenetic and genomic changes which may stimulate cancer progression. "Nano-epigenetics" and "nano-toxicity" are promising and rapidly developing fields in nanoscience and their future achievements might contribute to the development of nanoparticles of limited toxicity and side-effects.

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