Scientific Research Publishing

Journal of Biomaterials and Nanobiotechnology, 2017, 8, 220-228
http://www.scirp.org/journal/jbnb
ISSN Online: 2158-7043
ISSN Print: 2158-7027

Nanomaterials and Cell Interactions: A Review

Tenderwealth Clement Jackson[1*], Bernard Opatimidi Patani[2], Mary Blessed Israel[3]

[1]Department of Pharmaceutics and Pharmaceutical Technology, University of Uyo, Uyo, Nigeria
[2]Medical Department, Nigerian AGIP Oil Company, Port Harcourt, Nigeria
[3]Department of Biochemistry, University of Uyo, Uyo, Nigeria
Email: *clementjackson1@gmail.com

How to cite this paper: Jackson, T.C., Patani, B.O. and Israel, M.B. (2017) Nanomaterials and Cell Interactions: A Review. *Journal of Biomaterials and Nanobiotechnology*, **8**, 220-228.
https://doi.org/10.4236/jbnb.2017.84015

Received: August 6, 2017
Accepted: September 18, 2017
Published: September 21, 2017

Abstract

Nanotoxicology, a branch of bionanoscience focuses on the study of the hazardous interactions between nanomaterials and the ecosystem and ascertaining its consequent implications. Nanomaterial-cell interactions are dependent on numerous factors such as size, shape, type and surface coatings/charge of nanomaterials. These factors in association with cell membrane factors such as charge and formation of the protein corona influence the uptake and internalization of these particles leading to their potential toxicity. Understanding the different routes of exposure, their transport, behaviour and eventual fate is also of importance. Toxicities that occur to the living systems are consequences of various causes/dysfunctions such as ROS production, loss of membrane integrity, releases of toxic metal ions that bind with specific cell receptors and undergo certain conformations that inhibit normal cell function resulting in cytotoxicity, genotoxicity and possible cell necrosis. This paper attempts to review the available research pertaining to nanomaterial-cell interactions and their potential toxicity.

Keywords

Nanotoxicology, Nanomaterials, Cell, Cytotoxicity, Oxidative Stress, Genotoxicity

1. Introduction

Understanding the interactions between nanomaterials and the cell cannot be overemphasized in the areas of nanotoxicology and nanomedicine. Nanotoxicology, a branch of bionanoscience focuses on the study of the hazardous interactions between nanomaterials and the ecosystem and further ascertaining its consequent implications. Nanomaterials are unambiguously defined as materials having particles or constituents with external dimension in the nanoscale be-

tween 1 - 100 nm. They can either originate from combustion, manufacturing or naturally occurring processes. In recent times, there has been a steady exponential increase in the production of nanomaterials by combustion and manufacturing processes as a result of its exploitation in applications cutting across several industrial sectors and disciplines. A 30-fold increase in nano-based products between 2011 and 2015 and an approximate market sale of $1 trillion globally in 2015 have been reported [1]. Furthermore, there is a projected increase of total production of nanomaterials from an approximate 2300 tons in 2006 to 58,000 tons by the end of 2020 [2]. Consequently, there is a current elevation in the exposure of living things in the ecosystem to nanomaterials and there is prediction for continued increase. This has intensified the concerns of the potential toxicity arising from these exposures. In this paper, emphasis will be on the potential toxicity of these exposures to cells and the function of its components, *i.e.* DNA. The cell being the basic functional unit of living things would best be used for the study to ensure less complexity and maximal understanding of the mechanisms involved and the role of metabolism. However, due to the complexity of nanomaterial and cell interactions, the mechanism of action of nanomaterial toxicity is not yet fully understood but a proposed and accepted mechanism by which nanomaterials may induce cytotoxicity is through inducing reactive oxygen species (ROS) which can initiate oxidative stress which could subsequently lead to cytotoxicity, DNA damage, and other adverse effects. To get the basics, the composition of their physical, chemical and other properties that influence their toxicity must first be discussed and understood. Finding answers to questions such as: Is the toxicity reversible or irreversible? What is the relationship to exposure (threshold of effect)? Which sub-populations are susceptible? What are the target organs? Is the effect species specific? Are there trans-generational effects? What is the role of metabolism? etc. is also essential.

2. Determining Factors in Nanomaterial-Cell Interactions

Inorganic nanomaterials otherwise called nanoparticles/nanocrystals are composed of specific and unique physico-chemical properties which are factors that influence their complex interactions with cells. These include: 1) particle size and distribution; 2) surface area, charge and coatings; 3) shape/structure of particle; and 4) dissolution and aggregation. Other properties such as magnetic, optical, electronic, thermal and mechanical make them widely used in several applications and consumer products. These properties enhance their cell permeating ability and penetration of other biological barriers into living organisms.

2.1. Particle Size and Distribution

Research has shown higher degree of toxicity of nanomaterials in relation to their larger bulk particles thereby leading to the assumption that nano particles are more effective in causing damage. A direct correlation between nanoparticles size, its distribution in tissues and consequent toxicity has been reported [3].

2.2. Surface Charge and Coatings

Surface charge is a major determinant of nano particle dispersing features which plays an important role in binding to cell membrane, the absorption of ions and subsequent cellular uptake. Research reports enhanced toxicity due to increased surface charge of Iron Oxide (FeO) and Silver nanoparticles ($AgNO_3$) respectively while surface coatings indirectly affect aggregation and dissolution properties thereby enhancing the surface charge [4].

2.3. Shape and Structure of Particle

The morphology and shape of a nanoparticle are very important factors that influence their toxicity. Morphology, *i.e.* spheres, rods, truncated triangles, particles, cubes, wires, fields and coatings etc. affects the kinetics, transport and subsequent cellular uptake of nanoparticles. To buttress this fact, inhibition of *Escherichia coli* has been shown to be greater by triangular nanoplates in comparison to spherical- or rod-shaped Ag nano particles which could be due to high atom density of the triangular nano particles [5].

2.4. Dissolution and Aggregation

These properties are important in governing nanoparticles behavior and toxicity. Due to the fact that nanoparticles are not found isolated in nature, taking into perspective the added presence of other environmental stressors. Waste nanoparticles are released as aggregates and soluble ions into the environment. Dissolution and aggregation are processes that are largely influenced by size, surface properties and colloidal stability of which the later is in turn influenced by environmental stressors which include temperature, pH, and ionic strength thereby increasing exposure levels and subsequent toxicity. A study by showed silver nanoparticles exhibited high and rapid aggregation in media at high ionic strength [6].

3. Routes of Exposure, Transport and Fate of Nanomaterials

Synthesized nanomaterials are fast becoming a part of our everyday life due to our daily use of cosmetics, food packs, drugs, biosensors etc. to enhance drug delivery systems and odor-combating properties. This has spiked the rate of exposure to nanomaterials and their supposed toxic effects. It is therefore of essence to investigate and deeply understand the different routes of the body's exposure to these particles, their transport and their eventual fate and behavior in the body which influences their toxicity.

Nanomaterials can be released into the environment by intention or unintentionally through manufacturing processes such as atmospheric emissions and waste streams from production industries. Environmental exposure to nanoparticles in clothes, sunscreen, cosmetics, and health care products is directly related to their usage. Nanoparticles emitted settle on land and water and potentially contaminate ground and surface waters, soil and potentially become toxic

to aquatic life and plant products. Nanoparticles intentionally released into the environment by technological applications, diffuse releases from wear and spillage also greatly increase exposure.

Although nanomaterials from engineered processes are minimal, airborne particles increase inhalation exposure and could undergo aggregation into larger particles or chains thereby changing their composition and potential effect on entrance into the body system [7]. In the respiratory system, due to its high surface area/activity, unusual morphology and small diameters, enhanced toxicity based on nanostructure occurs. Nanoparticles have been found to have higher deposition rates in lungs of individuals with asthma/chronic obstructive pulmonary diseases than in healthy individuals [8].

It is suggested that on inhalation, nanoparticles deposit haphazardly on the alveolar surface, likely leading to a scattered chemo-attractant signal which results in reduced recognition and macrophage responses [9]. It has also been reported that there is decreased clearance of less than 25% of 50 - 100 nm particles within the first 24 hr after inhalation [8].

In relation to the skin, exposure could either be intentional or non-intentional. Use of lotions, cosmetics, wound dressing, detergents and clothes containing nanomaterials constitute intentional exposure e.g. use of sunscreen containing Nano TiO_2 and ZnO materials. Diffuse release from wear and abrasion of clothes when worn and washed also contribute to dermal exposure.

4. Nanomaterials Toxicity

As highlighted earlier, the potential toxic effects of nanomaterials on the ecosystem is influenced by its physiochemical properties such as type, size, surface area/coatings, charge etc. Toxicities that occur to the living systems are consequences of various causes/dysfunctions such as ROS production, loss of membrane integrity, releases of toxic metal ions that bind with specific cell receptors and undergo certain conformations that inhibit normal cell function resulting in cytotoxicity, genotoxicity and possible cell necrosis.

With respect to these observations, nanomaterials toxicity will be discussed based on the types and classes of nanomaterials, e.g. metallic, metal oxides, carbon nanotubes and quantum dots.

4.1. Metal and Metal Oxide Nanomaterials

Metallic nanomaterials and their oxides turn out to be the most used in industries and technological applications such as health, textiles and cosmetics. Gold nanoparticles, according to research, have been reported to be safe (not cytotoxic on cellular uptake) [10]. The group investigated cellular uptake and potential cytotoxicity of gold nanoparticles in human leukaemic cells and reported that these spherical shaped gold particles paired with different surface coatings were not toxic to human cells on exposure and uptake. However, although not found to be cytotoxic, gold nanoparticles have the capacity to cause cellular damage as

shown by a study on citrate-capped gold nanospheres [11]. The group reported their ability to aid the formation of abnormal act in filaments which resulted in reduced cell proliferation, adhesion and impaired motility.

Silver nanoparticles which are widely used for therapeutics due to their potent antimicrobial activity readily undergo ionization thereby enhancing their toxicity. Exposure to high levels of silver consistently over a long period causes argyria, breathing problems, lungs and throat irritation, stomach pains and skin allergic reactions. A group study reported that with increasing doses (10 - 75 μg/ml) of silver nanoparticles (15 - 30 nm) there was a decrease in cell viability over a period of 24 h and this was found to be likely mediated by oxidative stress due to more than a 10-fold increase of ROS levels in cells exposed to 50 μg/ml silver (15 nm) particles [3].

Another study examined the capacity of various nanoparticles and nanotubes to be cytotoxic and cause DNA damage and oxidative stress centering on metal oxide nanoparticles (CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_3O_4, Fe_2O_3) [12]. Results indicated a wide difference in the level of different metal oxide nanoparticles cytotoxicity. CuO nanoparticles were the most cytotoxic and genotoxic, TiO_2 was responsible for DNA damage, ZnO had adverse effects on cell viability and DNA, $CuZnFe_2O_4$ induced DNA lesions while iron oxide particles showed little or no cytotoxicity. CeO_2 particles are seen as non-cytotoxic and non-inflammatory to cells on uptake, but suppress ROS production and induce cellular resistance to external source of oxidative stress.

4.2. Carbon Nanotubes

Carbon nanotubes are widely used in applications for commercial products due to their exceptional nanostructure and properties, thereby increasing human and environmental exposure. This has engineered the investigation of the toxicity of these carbon nanotubes by several studies, especially the multi-walled carbon nanotubes (MWCNTs) mostly used due to its relative low cost. Some of these studies have reported the capacity of carbon nanotubes to cause inflammatory and apoptosis responses in human T cells [13] [14].

One study reported MWCNTs activation of genes involved in cellular transport, metabolism, cell cycle regulation, and stress response in human skin fibroblasts [13]. On examining the response of mouse embryonic stem cells DNA to MWCNTs uptake, another group reported that on accumulation, nanotubes had the ability to induce apoptosis and activate the tumor suppressor protein p53 within 2 h of uptake [14].

4.3. Quantum Dots

These are nanocrystals consisting 1000 to 100,000 atoms and are capable of emitting "quantum effects", *i.e.* prolonged fluorescence. Their exceptional optical and electrical properties make them valuable in the biomedical applications such as biomedical imaging, labeling neoplastic cells, DNA, and cell membrane receptors.

The skin is the most susceptible route of exposure for quantum dots to the body system and subsequently cells. A group study supporting this fact, reported the susceptibility of rat skin to quantum dots penetration is essentially limited to the topmost stratum corneum layers of unbroken skin [15]. A similar study also reported cytotoxicity of CdTe quantum dots with cysteamine and mercaptopropionic acid coatings on uptake by pheochromocytoma cells [16]. Cell necrosis was found to arise due to membrane bleeding and chromatin condensation. These studies have shown that quantum dots cytotoxicity can be minimized by regulating processing parameters during synthesis such as surface coatings, and UV light exposure [15] [16].

5. Mechanisms of Nanomaterial Toxicity

In response to the recent and proposed increase in the toxic exposure of cells to nanomaterials and particles, researchers have undertaken studies to determine and understand the different mechanisms through which these particles and their bulk counterparts interact with and affect the cells adversely. Due to their uniquely different properties, different nanomaterials exhibit different toxic potentials as seen in a study which examined (CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_3O_4, Fe_2O_3) nanometal oxides and reported CuO as the most potent genotoxic and cytotoxic nanometal oxide [12].

Results from *in vitro* assessment of nanoparticle toxicity have reported adverse effects at different levels of the cell structure. Certain endpoints measured include malformation, oxidative stress, stagnant growth/development, and gene expression. However, this is a sequential process whereby reactive oxyen species (ROS) and free radicals are generated which induce oxidative stress, lipid peroxidation, DNA damage and subsequently cell necrosis.

5.1. The Concept of Cellular Uptake

Cellular uptake is usually a two step process that includes binding to membrane receptors and transport/internalization. Certain factors such as nanoparticle charge, size, type of nanoparticle and the surface charge of the cell membrane play important roles in cellular uptake. The positive charge of nanoparticles has greatly influenced their uptake due to the fact that their electrostatic interactions with the negatively charged cell membrane are favourable.

However, recent findings prove that there has been cellular uptake of negatively charged particles which invariably suggests that electrostatic interactions only partly influence cellular uptake of nanoparticles. This therefore brings into view the role of the protein corona as a fundamental element in nanoparticle/cell interactions and subsequent toxicity. The formation and composition of the protein corona depends on the physico-chemical properties of the nano material/particle involved as it varies per particle. The protein corona influences cellular uptake of nanoparticles by creating an interface through modifying/masking the surface properties of a nanoparticle. Having discussed these basic surface in-

teractions resulting in cellular uptake, let's attempt to decipher the different mechanisms through which the potential toxic effects of nanoparticles occur on internalization.

5.2. Oxidative Stress

Oxidative stress is generally defined as a disproportion between the rate of production of ROS and the cells ability to reduce or mop it up, which may be either as a result of increased ROS production/a decrease in cells disease mechanism or both [17]. When there is uncontrolled/over production of ROS, the results include generation of protein radicals, induction of lipid peroxidation, Breakage of DNA strand and nuclei acids modification, modulation of gene expression and subsequent cell necrosis and genotoxicity.

Several authors have investigated the potential role of oxidative stress in Ag nanoparticles toxicity. A concentration-dependent increase in ROS production and oxidative stress was reported following a 7-day exposure to Ag nanoparticles (100 nm) at 10 and 100 μg/ml [17]. This was evaluated using antioxidant enzyme activity. A similar report showed concentration-dependent enzyme activities following the investigation of superoxide $\left(O_2^-\right)$ and stimulation of antioxidant defense mechanisms [18]. A third study reported instability of lysosomes resulting from initiation of apoptosis by Ag nanoparticles [19].

5.3. Genotoxicity

The *in vitro* genotoxic assessments of different nanoparticles have been reported. They include chromosomal fragmentation, DNA strands breaks, point mutuations, oxidative DNA adducts, alterations in gene expression profiles, potential mutagenesis and carcinogenesis [17]. Research has reported genotoxicity mediated by direct interactions of nanoparticles with DNA [20] and excess ROS production.

Regarding particle size, a group study reported that smaller sized nanoparticles were more genotoxic compared to their bulk counterparts [21]. Surface coatings of positively charged nanoparticles have also been found to enhance genotoxicity [22].

6. Conclusions

The exponential increase in the use of nanomaterials in consumer products has also led to uncontrolled increase in exposure and invariably increased cellular uptake, internalization and subsequent cytotoxicity to living systems. Nanomaterial-cell interactions are dependent on numerous factors such as size, shape, type and surface coatings/charge of nanomaterials. These factors in association with cell membrane factors such as charge and formation of the protein corona influence the uptake and internalization of these particles leading to their potential toxicity.

However, there are still aspects of nanomaterials cytotoxic mechanisms that are

yet to be understood, making it difficult to fully inhibit/combat their toxic effects. It is therefore recommended that further research be done as well as setting standard measures for their production and usage. Intentional and non-intentional releases of nanomaterials should also be monitored and regulated.

References

[1] Vance, M.E., Kuiken, T., Vejerano, E., *et al.* (2015) Nanotechnology in the Real World: Redeveloping the Nanomaterials Consumer Products Inventory. *Journal of Nanotechnology*, **6**, 1769-1780. https://doi.org/10.3762/bjnano.6.181

[2] Maynard, A.D. (2006) Nanotechnology: A Research Strategy for Addressing Risk.

[3] Carlson, C., Hussain, S.M. and Schrand, M. (2008) Unique Cellular Interaction of Silver Nanoparticles: Size Dependent Generation of Reactive Oxygen Species. *The Journal of Physical Chemistry B*, **112**, 13608-13619. https://doi.org/10.1021/jp712087m

[4] Baalousha, M. (2008) Aggregation and Disaggregation of Iron Oxide Particles: Influence of Particle Concentration. pH, and Natural Organic Matter. *Science of the Total Environment*, **407**, 2093-2101. https://doi.org/10.1016/j.scitotenv.2008.11.022

[5] Pal, S., Tak, Y.K and Song, J. (2007) Does the Antibacterial Activity of Ag Nanoparticles Depend on the Shape of the Nanoparticle? A Study of the Gram Negative Bacteria *Escherichia coli*. *Applied Environmental Microbiology*, **73**, 1712-1720. https://doi.org/10.1128/AEM.02218-06

[6] Romer, I., White, T., Baalousha, M., Chipman, K., Viant, M. and Lead, J. (2011) Aggregation and Dispersion of Silver Nanoparticles in Exposure Media for Aquatic Toxicity Tests. *Journal of Chromatography*, **1218**, 4226-4233. https://doi.org/10.1016/j.chroma.2011.03.034

[7] Lee, K.J., Nathathamby, P.D., Browning, L.M., Osgood, C.J. and Xu, X. (2007) *In Vivo* Imaging of Transport and Biocompatibility of Single Silver Nanoparticles in Early Development of Zebrafish Embryos. *ACS Nano*, **1**, 133-143. https://doi.org/10.1021/nn700048y

[8] Kreyling, W.G., Semmler-Behnke, M. and Moller, W. (2006) Ultrafine Particle-Lung Interactions: Does Size Matter? *Journal of Aerosol Medicine*, **19**, 74-83. https://doi.org/10.1089/jam.2006.19.74

[9] Paresh, C.R., Hongtao, Y. and Peter, P. (2009) Toxicity and Environmental Risks of Nanomaterials: Challenges and Future Needs. *Journal of Environmental Science and Health. Environmental Carcinogenesis and Ecotoxicology Reviews*, **27**, 1-35. https://doi.org/10.1080/10590500802708267

[10] Connor, E.E., Mwamuka, J., Gole, A., Murphy, C.J. and Wyatt, M. (2005) Gold Nanoparticles Are Taken up by Human Cells but Do Not Cause Acute Cytotoxicity. *Small*, **1**, 325-327. https://doi.org/10.1002/smll.200400093

[11] Pernodet, N., Fang, X. and Sun, Y. (2006) Adverse Effects of Citrate Gold Nanoparticles on Human Dermal Fibroblasts. *Small*, **6**, 766-773. https://doi.org/10.1002/smll.200500492

[12] Karlsson, H.L., Cronholm, P., Gustafsson, J. and Moller, L. (2008) Copper Oxide Nanoparticles Are Highly Toxic: A Comparison between Metal Oxide Nanoparticles and Carbon Nanotubes. *Chemical Research in Toxicology*, **21**, 1726-1732. https://doi.org/10.1021/tx800064j

[13] Ding, L., Stillwell, J., Zhang, T., *et al.* (2005) Molecular Characterization of the Cytotoxic Mechanism of Multi-Wall Carbon Nanotubes and Nano-Onions on Human

Skin Fibroblast. *Nano Letters*, **5**, 2448-2464. https://doi.org/10.1021/nl051748o

[14] Zhu, L., Chang, D.W., Dai, L. and Hong, Y. (2007) DNA Damage Induced by Multiwalled Carbon Nanotubes in Mouse Embryonic Stem Cells. *Nano Letters*, **s7**, 3592-3597.

[15] Zhang, L.W., Yu, W.W., Colvin, V.L. and Monteiro-Riviere, N. (2008) Biological Interactions of Quantum Dot Nanoparticles in Skin and in Human Epidermal Keratinocytes. *Toxicology and Applied Pharmacology*, **228**, 200-211.

[16] Lovric, J., Bazzi, H.S., Cuie, Y., Fortin, G.R., Winnik, F.M. and Maysinger, D. (2005) Differences in Subcellular Distribution and Toxicity of Green and Red Emitting CdTe Quantum Dots. *Journal of Molecular Medicine*, **83**, 377-385. https://doi.org/10.1007/s00109-004-0629-x

[17] Walters, C., Pool, E. and Somerset, V. (2016) Nanotoxicity in Aquatic Invertebrates. In: Larramendy, M.L. and Soloneski, S., Eds., *Invertebrates—Experimental Models in Toxicity Screening*, Intech, Croatia, 13-34. https://doi.org/10.5772/61715

[18] Orberholster, P.J., Musee, N., Noth, A.M., Chelule, P.K., Focke, W.W. and Ashton, P. (2011) Assessment of the Effect of Nanomaterials on Sediment-Dwelling Inveterbrate *Chironomus tentans* Larvae. *Ecotoxicology and Environmental Safety*, **74**, 416-423.

[19] Moore, M. (2006) Do Nanoparticles Present Ecotoxicological Risks for the Health of the Aquatic Environment? *Environment International*, **31**, 8350-8361.

[20] Landsiedel, R., Kapp, M.D., Schulz, M., Wiench, K. and Oesch, F. (2009) Genotoxicity Investigations on Nanomaterials: Methods, Preparation and Characterization of Test Material, Potential Artifacts and Limitations—Many Questions, Some Answers. *Mutation Research*, **681**, 241-258.

[21] Kim, Y.S., Kim, J.S. and Cho, H. (2008) Twenty Eight Day Oral Toxicity, Genotoxicity, and Gender Related Tissue Distribution of Silver Nanoparticles in Sprague-Dawley Rats. *Inhalation Toxicology*, **20**, 575-583. https://doi.org/10.1080/08958370701874663

[22] Liu, Y., Xia, Q., Zhang, S., *et al*. (2004) Genotoxicity of Magnetic Iron Oxide Nanoparticles with Different Particle Sizes and Surface Coatings. *Nanotechnology*, **25**, Article ID: 425101. https://doi.org/10.1088/0957-4484/25/42/425101