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Genetic and epigenetic effects of nanoparticles

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ABSTRACT

Human beings are exposed to extremely small particles mostly through surrounding atmosphere. Exposure to engineered NPs can happen through pathways like inhalation, dermally and ocularly. The wide spread use and applications such as oral administration through food or drinking water, skin absorption through sunscreen or cosmetics application, injection through medical procedures presents many potential problems. The fate and risk may differ through different exposure pathways.

In most of the studies it has been found that over 90% of orally administrated engineered NPs were excreted through fecal matter by animals. However, with their small sizes, the retention of NPs is found in the kidney and liver. The little size and big surface area of NPs facilitates the production of free radicals, increased oxidant production, leading to genetic and epigenetic effects.

KEY WORDS: Epigenetic, Nano particles, genotoxicity.

1. INTRODUCTION

Tissue culture analysis in animal models, demonstrates that increased oxidant production contributes significantly to the cytotoxicity and genotoxicity associated with NP exposure. The biological impact and biokinetic distribution of NPs are affected by many parameters including size, chemical constitution, surface structure, dissolving capacity, shape, and augmentation. These criteria can convert cellular uptake, translocation from exposed organs to the targeted sites and the severity of the tissue injury. The organs and tissues targeted are such as endothelium, blood cells, spleen, liver, nervous system, heart and kidney.

Negative health effects of Nps: Nanoparticles can influence basic cellular processes, such as proliferation, metabolism, and death. Many diseases can be associated with disfunction of these basic processes. For example, cancer results from uncontrolled cell multiplication, while neurodegenerative diseases are caused in part by premature cell death. Increased oxidant production had its effect in many diseases, including cardiovascular and neurological disease, pancreatitis, and cancer. Severe inflammation is assumed to be the initiating step in the appearance of autoimmune diseases associated by contact with nano particles, like silica and asbestos.

Genetic consequences of NPs: The genetic effects of NPs include DNA damage, possibly leading to mutations, DNA strand breaks and chromosomal aberrations. The mechanism of NPs genetic effects are as follows: (a) direct binding to the DNA: some NPs are capable of localizing within the nucleus, directly interacting with the DNA molecule, (b) direct attachment to DNA associated proteins: where the NPs do not physically interact with the DNA molecule, but with other cellular proteins which are associated with the chromatin structure or DNA replication process; (c) indirect cellular responses: oxidative stress, inflammation and aberrant signalling activation.

Oxidative stress generation: Oxidative stress is a response to cell injury, and can also occur due to cellular respiration, general metabolism, myocardial ischemia, swelling in the body, and metabolism of foreign compounds. Both natural and laboratory studies have shown that nanoparticles with various constitutions like spherical fullerenes, carbon nanotubes, quantum dots, and automobile burn outs create reactive stress that damage cells by peroxidising lipids, altering proteins, disrupting DNA, interfering with signalling functions, and modulating gene transcription.

Inflammation: The normal response of the body to injury is inflammation. When generated in moderation, inflammation stimulates the regeneration of healthy tissue, however when in excess, it can cause a disease. Exposure to small nanoparticle results in inflammation, with particle dimension and composition being the most important factors. A complex series of intracellular and extracellular events control inflammation. Some nanoparticles can produce cell death via mitochondrial damage without inflammation.

DNA damage: Exposure to the nanoparticles overwhelms antioxidant defense system resulting in the destruction of cell bio molecules like DNA, leading to heritable mutations. For example, the modification of histones which occur opens the coiled DNA and allows its alteration.

Nanoparticles of various materials (diesel, carbon black, welding fumes, transition metals) are genotoxic in humans or rats. Oxidative DNA damage markers showed higher levels on workdays for bus drivers from urban areas compared to bus drivers from rural areas. Nanoparticles can directly produce reactive oxygen species on the surfaces or by activation of macrophages. Overall, the creation of oxidative species leads to more inflammation and increased antioxidant production. When macrophages are activated it leads to modulation in intracellular calcium concentration that in turn activates further the reactive oxygen species production, which in turn enhances further calcium signaling by oxidation of calcium pumps in the endoplasmic reticulum, leading to calcium depletion.

Intracellular calcium modulation results in impaired motility and reduced macrophage phagocytosis. Nanoparticles that are non-phagocytized are likely to ingress and interact with epithelial cells, thus enhancing inflammation. Ultimately the interaction of nanoparticles with cells may lead to DNA modifications, cell injury, and disease.

The Epigenetic Effects of NPs: Epigenetic effects generally bring heritable changes in phenotypes or gene expression without a change of DNA sequences. Epigenetic effects involve inducing alterations in DNA methylation patterns, posttranslational changes of histones tails, chromatin remodeling and non-coding RNA. If these changes persist through cell division, heritable altered gene expression pattern will occur. Several NPs have shown epigenetic effects and may lead to health risks. Epigenetic properties can be deployed by environmental agents and this has increasing evidence of epigenetic deregulation of gene expression in several human diseases, including cancer, cardiovascular diseases, autism spectrum disorders, autoimmune diseases, and neuro degeneration, among others.

DNA methylation: Methylation on cytosines and their later interaction with methyl-CpG binding proteins (MBDs) act as regulatory marks to induce chromatin configuration change and inhibit the entry of the transcriptional machinery, thus altering gene expression. The transfer of a methyl group to cytosine is catalyzed by DNA methyl transferases (DNMTs). In mammals DNMT1 is mostly concerned with the maintenance of DNA methylation patterns during development and cell division, where as DNMT3a and DNMT3b are the *de novo* methyl transferases and establish DNA methylation patterns during early development. By activation of DNMT3a DNA methylation is induced by DNMT3L, while DNMT2 is concerned with the methylation of transfer RNA.

Promoter hyper methylation is generally related with gene silencing with a few exceptions where intragenic methylation might also have a role in regulating gene expression. Silica nano particles (SiO_2 NP) are highly stable and can bio accumulate in the natural environment. SiO_2 NPs are a group of NPs that has great potential for scientific, biological, and medical research applications.

Micro RNA induced gene expression change: Major part of the genome is transcribed into RNA with a significant portion of non-coding RNA (ncRNA) that function as structural, catalytic, or regulatory RNAs, than the encoding proteins.. The functions of most of the newly identified ncRNAs are yet to be clarified but emerging evidences has shown that ncRNAs play an important role in chromatin remodeling and epigenetic control of transcription. MicroRNAs are a group of small ncRNAs that mediate gene silencing after transcription of nucleotide sequence through degradation of mRNA or inhibition of mRNA translation. A complicated feedback network of mi RNAs and other epigenetic pathways appears to repress gene expression including those signal molecules and thus are critical for many cellular pathways, and to organize the whole gene expression profile.

Treatment: Regarding the treatment of harmful health effects caused by nanoparticles cytotoxicity, antioxidants, anti-inflammatory drugs, and metal chelators show promising effects. Instillation of nanoparticles into the lungs of rats together with an antioxidant (nacystelin) showed the reduction of inflammation up to 60% in comparison to those that are exposed to nanoparticles alone. Antioxidant therapy protects animal species against the development of hypertension, arteriosclerosis, cardiomyopathies, and coronary heart disease. It thus provides further evidence of the relation between the oxidative stress response and cardiovascular effects. The harmful health effects of transition metals can be diminished by metal chelators.

2. CONCLUSION

Many toxicology studies are lacking data showing NP accumulation and dissolution which occurs in sample media, let alone the changes in bioavailability and toxicity. The proposals for the use of OECD standardized methods are put forward to analyse the genotoxicity of NPs, and they should be employed in near future. The reactions between nanoparticles and natural organic matter that occurs during waste processing, results in a Nano scale coating of the nano materials, which dramatically changes their surface chemistry, aggregation, deposition, and toxic properties. Engineered nanoparticles in natural systems are subject to a dynamic physical and chemical environment; therefore the toxicity analysis using their "as manufactured" state might not be thorough and comprehensive. More detailed and thoughtful design is needed for accurate risk assessment of NPs. Negative effects on cells especially cytotoxicity and cell death are caused due to NPs and their interactions with organelles and macromolecules. Even though the toxicity of NPs can be considered useful for cancer therapy, at the same time it seems to be harmful for non-cancer cells. Recent studies reveal that epigenetic and genomic changes caused by nanoparticles may stimulate cancer progression also. The rapidly developing and promising fields in Nano science are "Nano-epigenetics" and "nano-toxicity" that require much consideration.

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